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Original Articles

REACTIONS TO ANTIPNEUMOCOCCAL RABBIT SERUM*†

XI. NEUTRALIZATION OF CIRCULATING POLYSACCHARIDE BY SERIAL SMALL INCREMENTS OF SPECIFIC ANTISERUM WITHOUT PRODUCING REVERSED PASSIVE ANAPHYLAXIS

XII. NEUTRALIZATION OF POLYSACCHARIDE PREVENTS ACUTE ANAPHYLAXIS FROM NORMALLY SHOCKING DOSES OF ANTISERUM

XIII. REINJECTION OF AN EXCESS OF POLYSACCHARIDE RESENSITIZES GUINEA PIGS TO NORMALLY SHOCKING DOSES OF ANTISERUM

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PROMPT untoward reactions to therapeutic doses of antipneumococcal rabbit serum are common. Conventional anaphylaxis is the accepted mechanism for reactions which occur when skin reactions to serum are positive. However, results of tests for sensitivity were negative in nearly 80 per cent of a large series of reactions to antipneumococcal serum.[1] It is thought that reversed passive anaphylaxis mediates reactions to antiserum which occur when tests for sensitivity are negative.[2] Reversed passive anaphylaxis did not occur in guinea pigs when the shocking dose of antiserum was reduced to less than 0.03 ml. and sensitizing doses of polysaccharide and the interval between sensitizing and shocking doses were constant.[3] Reversed passive anaphylaxis did not occur when the injection rate of small shocking doses of antiserum was increased beyond 180 seconds.[4] This is the report of three experiments designed to throw additional light on the problem of the prevention of reversed passive anaphylaxis. Experiments XI, XII, and XIII were designed to show three things: first (Experiment XI), that serial, small increments of type-specific antiserum would neutralize the circulating polysaccharide in guinea pigs without producing obvious reversed passive anaphylaxis; second (Experiment XII), that acute anaphylaxis would not follow normally shocking doses of antiserum after neutralization of circulating polysaccharide; and third (Experiment XIII), that reinjection of an excess of polysaccharide would resensitize the guinea pigs to normally shocking doses of antiserum.

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TABLE IA. EXPERIMENT XI. NEUTRALIZATION OF CIRCULATING POLYSACCHARIDES WITHOUT PRODUCING REVERSED PASSIVE ANAPHYLAXIS

NO. ANIMAL	AMOUNT TYPE 8 POLYSAC. MG.	ELAPSED TIME MIN.	*NEUTRALIZING ANTISERUM ML.	SPEED OF INJ. SEC.	C.MM. PPT. IN J-TUBE	†	‡SHOCKING DOSE OF ANTISERUM ML.	ANAPHYLACTIC REACTION	DIED 8 HRS.
1	0.1	20	0.05	180	9.00				
		40	0.10	180	7.60				
		60	0.15	180	3.06				
		80	0.20	30					
		100	0.25	30	0.00				
		120	0.30	30	0.00		2.0	None	Yes
2	0.1	20	0.05	180	6.52		Died before shocking dose		
		40	0.10	180	1.80				
		60	0.15	180	1.12				
		80	0.20	30	0.00				
		100	0.25	30	0.00				
		120	0.30	30	0.00				
3	0.1	20	0.05	180	7.61				
		40	0.10	180	4.64				
		60	0.15	180	1.23				
		80	0.20	30	0.00				
		100	0.25	30	0.00				
		120	0.30	30	0.00		2.0	None	Yes
4	0.1	20	0.05	180	6.55				
		40	0.10	180	0.96				
		60	0.15	180	0.00				
		80			0.00		2.0	None	Yes

TABLE IB. EXPERIMENT XII. RESISTANCE TO NORMALLY SHOCKING DOSES OF ANTISERUM AFTER NEUTRALIZATION OF POLYSACCHARIDE

*Saline added to make uniform dose of 0.3 ml.

†No animal had anaphylactic signs, but all were very listless.

‡Lot No. 418, antipneumococcal Type 8 rabbit serum, 3400 units ml. used for shocking and neutralizing in all experiments.

Experiment XI is summarized in Table IA.

Method.—Each of four guinea pigs was given a sensitizing dose of 0.1 mg. of Type 8 pneumococcal polysaccharide. Each animal was then given increments of 0.05 ml. of antiserum intravenously every twenty minutes for three to six doses. Each increment was diluted with physiologic saline, if necessary, to make a uniform dose of 0.3 milliliter. Each of the first three injections took approximately 180 seconds. Each subsequent injection was given rapidly, in less than thirty seconds. Lot #418, Type 8 antipneumococcal rabbit serum, 3400 units/ml., was used throughout.

A corresponding amount, 0.3 ml., of blood was withdrawn from the jugular veins, just before the antiserum was injected, for titration of circulating polysaccharide. Guinea pig serum, 0.033 ml., was mixed with 0.1 ml. of antiserum and 0.067 ml. of saline in a capillary J-tube,[5] incubated, and centrifuged. The resulting precipitate was measured in cubic millimeters.

Results.—The titrations showed that each increment of antiserum reduced the amount of detectable circulating polysaccharide. No polysaccharide persisted after the second increment in one animal, after the third increment in

two, and after the fourth in another. Each animal became progressively more listless. One died after the final neutralizing dose of antiserum. None showed the slightest trace of anaphylaxis, in spite of rapid injection of the later and larger doses of antiserum.[4]

Experiment XII is summarized in Table IIB.

Method and Results.—A predetermined shocking dose of 2.0 ml. Type 8 antipneumococcal rabbit serum was given intravenously, immediately after the last sample of blood was withdrawn for polysaccharide titration. There was no trace of acute anaphylaxis following this large, rapidly injected dose of antiserum. However, all the animals were dead the next morning. Necropsy showed no evidence of acute anaphylaxis.

TABLE IIA. SALINE CONTROLS

NO. ANIMAL	AMOUNT TYPE 8 POLYSAC. MG.	ELAPSED TIME MIN.	AMOUNT SALINE CONTROL ML.	C.MM. PPT. IN J-TUBE	*	†SHOCKING DOSE OF ANTISERUM ML.	ANAPHYLACTIC REACTION	DIED 8 HRS.
1	0.1	20	0.3	7.71				
		40	0.3	14.11				
		60	0.3	9.96				
		80	0.3	2.18				
		100	0.3	3.89				
		120	0.3	5.23		2.0	Mod.[1]	Yes
2	0.1	20	0.3	6.11				
		40	0.3	10.72				
		60	0.3	6.36				
		80	0.3	7.66				
		100	0.3	6.52				
		120	0.3	4.28		2.0	Mild[2]	Yes

TABLE IIB. NONSPECIFIC ANTISERUM CONTROLS. AMOUNT NONSPECIFIC ANTISERUM

1	0.1	20	0.05‡	4.50				
		40	0.1	4.56				
		60	0.15	3.67				
		80	0.2	2.55				
		100	0.25	8.45				
		120	0.3	4.03		2.0		A.D.[3]
2	0.1	20	0.05	2.68				
		40	0.1	3.32				
		60	0.15	3.82				
		80	0.2	2.33				
		100	0.25	3.60				
		120	0.3	3.18		2.0	Mod.	Yes

TABLE IIC. POSITIVE SPECIFIC CONTROL

1	0.1	60			[4]	2.0	A.D.	

*No animal had anaphylactic signs, but all were very listless.

†Lot No. 418, antipneumococcal Type 8 rabbit serum, 3400 units/ml., used for shocking and neutralizing in all experiments.

‡Saline added to make uniform dose of 0.3 ml.

[1]Sneezing, scratching, ruffled hair, marked dyspnea, defecation, urination, mild convulsion. Recovery.

[2]Sneezing, ruffled hair, moderate dyspnea, scratching, no convulsion. Recovery.

[3]Anaphylactic death.

[4]Animal lively.

Saline controls are summarized in Table IIA. Note that there was no marked reduction in circulating polysaccharide although the values varied widely. Both animals had typical moderate anaphylactic reactions. Both recovered from the acute reaction, but were dead the next morning. Both animals were about as listless as those in Tables IA and III before the shocking doses of antiserum were given. Nonspecific antiserum controls are summarized in Table IIB. Both animals responded like the saline controls except that one had immediate fatal anaphylaxis. Both became listless before the shocking doses of antiserum were given. The one that survived the immediate anaphylaxis was dead the next morning. The predetermined shocking dose is illustrated in Table IIC.

TABLE III. EXPERIMENT XIII, RESENSITIZATION WITH POLYSACCHARIDE AFTER NEUTRALIZATION OF SENSITIZING POLYSACCHARIDE WITH INCREMENTS OF ANTISERUM

NO. ANIMAL	AMOUNT TYPE 8 POLYSAC. MG.	ELAPSED TIME MIN.	*NEUTRALIZING ANTISERUM ML.	SPEED OF INJ. SEC.	C.MM. PPT. IN J-TUBE	†	‡SHOCKING DOSE OF ANTISERUM ML.	ANAPHYLACTIC REACTION	DIED 8 HRS.
1	Sensitizing								
	0.1	20	0.05	180	6.06				
		40	0.10	180	6.08				
		60	0.15	180	.66				
		80	0.20	30	0.00				
		100	0.25	30	0.00				
		120	0.30	30	0.00				
	Resensitizing								
	0.1	122							
		165		30	1.80		2.0	Mod.[1]	Yes
2	Sensitizing								
	0.1	20	0.05	180	8.38				
		40	0.10	180					
		60	0.15	180	3.52				
		80	0.20	30	1.85				
		100	0.25	30	0.00				
		120	0.30	30	0.00				
	Resensitizing								
	0.1	122							
		165		30	0.00		2.0	±[2]	Yes
3	Sensitizing								
	0.1	20	0.05	180	3.06				
		40	0.1	180	2.04				
		60	0.15	180	1.55				
		80			0.80				
	Resensitizing								
	0.1	82							
		125		30	1.40		2.0	Mod.[1]	Yes

*Saline added to make uniform dose of 0.3 ml.

†No animal had anaphylactic signs, but all were very listless.

‡Lot No. 418 antipneumococcal Type 8 rabbit serum, 3400 units/ml. used for shocking and neutralizing in all experiments.

[1]Sneezing, scratching, ruffled hair, marked dyspnea, defecation, urination, mild convulsion, recovery.

[2]Sick—none of symptoms of.[1]

Experiment XIII is summarized in Table III.

Method.—Sensitizing doses of polysaccharide and neutralizing increments of antiserum were given to three guinea pigs, as in Experiment XI.

Circulating polysaccharide was completely neutralized in two animals and was markedly reduced in the third. No trace of anaphylaxis followed

any of the neutralizing doses. The second increment of antiserum did not reduce the polysaccharide precipitate in Animal #1.

A resensitizing dose of 0.1 mg. of polysaccharide was given intravenously after the last sample of blood was withdrawn for titration. Circulating polysaccharide was titrated again just before the shocking dose. Animals #1 and #3 had 1.8 and 1.4 c.mm. of precipitate, respectively. Animal #2 showed no precipitate, in spite of the resensitizing dose of polysaccharide.

Forty-five minutes later a normally shocking dose of 2.0 ml. of antiserum was given each animal intravenously. Animals #1 and #3, which had circulating polysaccharide, had moderately severe anaphylactic reactions. The signs in Animal#2, which had no circulating polysaccharide, were equivocal and not typical of anaphylaxis.

DISCUSSION

The results of Experiments XI, XII, and XIII show, respectively: first, that serial small increments of type-specific antiserum neutralize circulating polysaccharide without producing reversed passive anaphylaxis; second, that acute anaphylaxis does not follow normally shocking doses of antiserum after neutralization of circulating polysaccharide, and third, that reinjection of an excess of polysaccharide resensitizes guinea pigs to normally shocking doses of antiserum. Apparently, the reinjection of polysaccharide must produce an excess of circulating polysaccharide in order to resensitize. Neutralization of the resensitizing dose of polysaccharide in Animal #2, Table III, was attributed arbitrarily to the accumulated increments of antiserum.

The rapid injection of antiserum produces anaphylaxis in the presence of significant amounts of circulating polysaccharide.[4] The last three increments of neutralizing antiserum were given rapidly in Experiments XI and XIII, Tables IA and III, without reaction. These data offer further support to the belief that circulating polysaccharide is the mediator of reversed passive anaphylaxis.[4, 6] This is at variance with the theory of Kellett,[7] Van den Ende,[8] and others that reversed passive anaphylaxis is mediated by antigen fixed to tissue cells.

No effort was made to determine the cause of the delayed deaths of the test and control animals. Those which were given saline and nonspecific serum seemed just as sick as the test animals before the shocking doses of antiserum. The experimental procedure was conducive to shock. Each animal seemed to recover from the anaphylactic reactions during the periods of observation, except the two which died promptly.

These experiments permit, with some repetition, the following comments: A negative cutaneous reaction to antiserum does not lessen the chance of reversed passive anaphylaxis. Nearly 80 per cent of a large series of reactions to antipneumococcal horse serum had negative skin reactions.[1] On the other hand, detectable amounts of circulating polysaccharide do predispose to reversed passive anaphylaxis.[5] Circulating polysaccharide should be titrated

before antiserum is given.[3] Antiserum should be given to pneumonia patients slowly[4] and in small increments (Experiment XI) until circulating polysaccharide has disappeared (Experiments XI and XIII). Therapeutic doses of antiserum should not be given until then.

SUMMARY

1. Circulating pneumococcal polysaccharide can be neutralized in vivo by serial small increments of type-specific antiserum without producing anaphylactic shock.

2. When circulating polysaccharide has been neutralized, guinea pigs tolerate normally shocking doses of antiserum without obvious reversed passive anaphylaxis.

3. Additional evidence is offered to support the belief that circulating polysaccharide mediates reversed passive anaphylaxis to type-specific antipneumococcal rabbit serum.

4. Circulating polysaccharide should be determined before therapeutic antiserum is given to pneumonia patients. If present, the circulating polysaccharide should be neutralized by small serial doses of antiserum, given slowly, before therapeutic doses are given.

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REACTIONS TO ANTIPNEUMOCOCCAL RABBIT SERUM*

XIV. Two Cases of Mild Reversed Passive Anaphylaxis

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REACTIONS to antipneumococcal rabbit serum are thought to be due to reversed passive anaphylaxis when skin and conjunctival tests for sensitivity are negative.[1] Circulating polysaccharide seems necessary for reversed passive anaphylaxis in guinea pigs.[2] Circulating polysaccharide is thought to be an ominous finding in pneumococcal pneumonia.[3] The determination of circulating polysaccharide before serum therapy has been advocated as a precaution against reversed passive anaphylaxis.[2] Circulating polysaccharide should be neutralized, if found, by small increments of antiserum before therapeutic doses are given.[2]

This is the report of two cases of pneumococcal pneumonia who had negative reactions to antiserum and reversed passive anaphylaxis after antipneumococcal rabbit serum.

Case 1.—A white male, 35 years of age, had a sudden onset of typical lobar pneumonia eighteen hours before admission. Blood and sputum cultures were positive for Type 2 pneumococci. He failed to respond to sulfadiazine, sulfathiazole, sulfamerazine, and penicillin in large doses. His Type 2 pneumococcus was completely resistant to penicillin, 5 units per milliliter. A precipitate of 2.76 c.mm. was obtained from 1.0 ml. of his serum by the addition of 0.1 ml. of commercial Type 2 antipneumococcal rabbit serum, in saline, in the capillary J-tube three days after admission.

The pneumonia, present in the middle lobe on admission, extended to the upper lobe in a few days. Some slightly cloudy sterile fluid was removed from the right base on the seventh and ninth days. On the eleventh day the temperature was 103° F. The Francis test with polysaccharide and the conjunctival reaction with Type 2 antipneumococcal rabbit serum were negative. The endermal reaction was not recorded. He wheezed a little shortly after a test dose of 0.5 ml. of antiserum in 20 ml. of physiologic saline intravenously. This subsided spontaneously. Wheezing began promptly when a second similar test dose was started an hour later. This was relieved by 0.2 ml. of Adrenalin. One hour later, 0.1 ml. of antiserum injected intravenously was followed promptly by asthma and a rectal temperature of 106° F. Adrenalin, 0.2 ml., gave relief.

A desensitizing, polysaccharide neutralization, program was begun after the third bout of wheezing. The first dose was 0.05 milliliter. This was followed by thirteen subcutaneous increments of 0.05 ml. of a 1:10 dilution of the antiserum in twelve hours. Next, hourly increments of the undiluted antiserum were given subcutaneously. The first dose was 0.1 ml., followed by 0.15, 0.20, 0.30, and 0.5 milliliter. Next, undiluted increments of antiserum were given intravenously every hour as follows: 0.1, 0.2, 0.4, then 1.0 milliliter. There were no reactions to any of these injections, a total of about 20,000 units. After the 1.0 ml. dose, 60,000 units in 1,500 c.c. of physiologic saline was given intravenously, slowly. His temperature rose to 104.5° F. transiently, but there were no other allergic reactions. By the next morning his temperature was normal. He seemed much improved. Ten days later he had mild serum sickness, characterized by stiffness and soreness in the jaws, neck, hands, wrists, and forearms, and swelling and itching of the hands and arms. This subsided without treatment and did not become a problem. He recovered slowly but uneventfully and completely.

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CASE 2.—A Negro male, 56 years of age, had a sudden onset of typical pneumonia one week before admission. Sputum, throat and blood cultures were positive for Type 3 pneumococcus. The blood culture was negative on the third hospital day. On the fourth day 2.70 c.mm. was precipitated from 2.0 ml. of his serum by 0.1 ml. of commercial Type 3 antipneumococcal rabbit serum, in saline, in the capillary J-tube. He did not improve after large doses of sulfadiazine and penicillin. The organism was susceptible to penicillin, 0.125 units per milliliter.

On the fifth hospital day his temperature was 102° F. The conjunctival reaction to 1:10 dilution of Type 3 antipneumococcal rabbit serum was negative. The endermal reaction to 0.1 ml. of undiluted antiserum was equivocal. The intravenous reaction to 1.0 ml. of a 1:10 dilution of the antiserum was negative. The undiluted serum, 1.0 ml., was given over a period of five minutes. There was no immediate reaction.

One hour later 50,000 units of undiluted serum were given intravenously, slowly, in ten minutes. Five minutes later he became acutely dyspneic. He seemed unable to exhale. There were no asthmatic squeaks. His blood pressure rose from 110/70 to 170/90, the pulse rate from 100 to 150 beats per minute. Adrenalin injected subcutaneously gave prompt relief. Fifteen minutes later his rectal temperature was 104.8° F. The temperature, pulse, and blood pressure returned to previous levels in about three hours. The next (sixth) day he was given 0.2 ml. of 1:10 antiserum, then 1.0, 2.0, and 4.0 ml. of undiluted serum subcutaneously at intervals of thirty to forty-five minutes. The last dose was followed by an increase in pulse from 96 to 120 beats per minute and blood pressure from 130/80 to 170/80. One hour later he was given 4.0 ml. again. An hour later he was given 6.0 ml. There were no reactions.

One hour and a half later he was given 15.0 ml. of the undiluted antiserum intravenously. He became apneic almost immediately. The pulse and blood pressure increased at once. He was relieved by Adrenalin promptly. On the seventh day his rectal temperature was 99.6° F. On the eighth day his temperature rose to 101° F. at noon. Desensitization, polysaccharide neutralization, with antiserum was begun with 0.1 ml. of the 1:10 dilution, subcutaneously. Each dose was doubled every hour, until 1.0 ml. was given. The same program was followed with the undiluted serum, until a dose of 2.0 ml. had been given. This dose was repeated every hour until midnight of the eighth day. The total antiserum at that time was 200,000 units.

On the ninth day his temperature was 100.2° F. at noon. He was given five doses of 2.0 ml. of undiluted serum subcutaneously between 2:00 P.M. and 11:00 P.M. The next day his temperature was 100.6° F. On the eleventh day he was given a total of 17 ml. of undiluted serum in six doses between 2:00 P.M. and 11:00 P.M. He had no reactions to the antiserum given on the eighth, ninth, or eleventh days. He was not cured by the serum therapy.

He did not improve any more until operation for lung abscess on the twenty-seventh day. His recovery was uneventful thereafter. Streptomycin, large doses of penicillin, and sulfamerazine were tried unsuccessfully prior to the operation.

DISCUSSION

Chemotherapy has not entirely eliminated the need for antiserum in the treatment of pneumonia. Both cases had pneumococcal pneumonia, positive blood and sputum cultures, circulating polysaccharide, unsatisfactory responses to combined sulfonamide and penicillin therapy, negative skin and conjunctival reactions to antiserum, dyspnea, and thermal reactions following injections of antiserum. Adrenalin relieved the reactions promptly.

In Case 1 subcutaneous increments of diluted, then undiluted, serum followed by intravenous increments, permitted the administration of therapeutic doses of antiserum without anaphylaxis. This did not prevent the appearance of the delayed serum sickness type of reaction. The serum seemed to be responsible for his recovery.

In Case 2 the conventional precautions, including the preliminary intravenous test doses of 1.0 ml., did not prevent the prompt anaphylactic type of reaction to 50,000 units of antiserum. A desensitizing, polysaccharide-neutralization program was partially effective, but less so than in Case 1. He had a second anaphylactic response to 15.0 ml. of the antiserum, although he had tolerated a 6.0 ml. dose without reaction. Large total doses of more than 300,000 units of antiserum were possible by administering serial 2.0 ml. doses subcutaneously. Antiserum did not cure him because of the complicating lung abscess. His maximal temperature after serum, however, was less than 101° F.

Circulating polysaccharide may be assumed to be present in a pneumonia patient to whom it is necessary to give antiserum. There will be exceptions, of course. This implies failure of chemotherapy, deficient antibody production, a poor prognosis without antiserum,[3] or complications. Yet circulating polysaccharide is the factor most conducive to reversed passive anaphylaxis.[2, 4] Cutaneous and conjunctival tests are of no value in predicting this type of anaphylaxis, since they were negative in nearly 80 per cent of a large series of reactions to antipneumococcal serum.[5] Skin and conjunctival reactions indicate sensitivity to rabbit serum. They do not detect circulating antigen (the "E-E" phenomenon[6] has not been noted with antipneumococcal serum in this clinic).

Detectable circulating polysaccharide is more common than has been supposed.[3] Serum from twelve of fifteen other cases yielded from 0.25 to 16.8 c.mm. of precipitate in the capillary J-tube. Types 1, 2, 3, 6, 17, and 33 were represented.

The following procedures are recommended before giving serum to a patient with pneumococcal pneumonia: type the offending organism; perform skin and conjunctival tests with antiserum; estimate the amount of circulating polysaccharide by precipitating from the patient's serum with antiserum;[4] if it is present, neutralize the polysaccharide by small increments of antiserum;[2] do not give therapeutic dose of antiserum until polysaccharide has been neutralized. A safe, first neutralizing dose and the proper route of administration have not been determined for humans. In the guinea pig the intravenous dose must be less than 100 units.[7] It would seem wise to start with one unit of antiserum, diluted with saline, given slowly, intravenously.

The cases reported were treated before the neutralization experiments were done,[2] so polysaccharide determinations were not used to determine when therapeutic doses could be given.

SUMMARY

1. Two cases of pneumococcal pneumonia had mild, reversed, passive anaphylaxis from small doses of antiserum. Each had an excess of circulating polysaccharide.

2. Effective hyposensitization is described.

3. Antiserum should be given slowly and in small increments when circulating polysaccharide is present. Therapeutic doses of antiserum should not be given until the circulating polysaccharide has been neutralized by the small increments of antiserum.

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A COMPARATIVE STUDY OF THE ACTION OF VARIOUS SYMPATHOMIMETIC AMINE AEROSOLS IN COUNTERACTING THE DYSPNEA AND BRONCHOSPASM INDUCED BY HISTAMINE AND BY ACETYL-BETA-METHYLCHOLINE*†

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THERE has developed a widespread clinical interest in the use of aerosols of various sympathomimetic amines for the management of bronchial asthma. Of these substances, three are in common use: epinephrine hydrochloride 1:100 U.S.P., Vaponefrin (a 2.25 per cent solution of specially prepared racemic epinephrine hydrochloride), and Isuprel [1-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol] hydrochloride in a 1:200 dilution. To determine the relative efficiency of these aerosols as antihistaminic or anticholinergic agents, we measured in the laboratory their ability to prevent the occurrence of the dyspnea and bronchospasm which follows the intravenous administration of histamine and of acetyl-beta-methylcholine to sensitive asthmatic subjects. By the same method we measured the protecting ability of Isuprel in a 1:100 dilution and of Neo-Synephrine (1-alpha-hydroxy-beta-methylamino-3-hydroxy ethylbenzene) hydrochloride in a 1:100 solution. The aerosols were produced by handbulb nebulization with the Vaponefrin nebulizer. The dosage of each therapeutic or protecting agent consisted of six deep inhalations of the specific aerosol in question.

The use of epinephrine hydrochloride as an aerosol in the management of bronchial asthma was first proposed by Ephraim in 1910,[1] but for the next quarter century only the 1:1,000 dilution was employed. Needless to say, the necessity of nebulizing large quantities of this solution rendered these techniques of little clinical value. In 1935, Graeser and Rowe[2] introduced the 1:100 dilution of epinephrine hydrochloride, which proved efficacious in relaxing asthmatic bronchospasm even when extremely small volumes of solution were employed. This advance in therapeutics was of immense importance. The early development of this technique was reviewed by Graeser in 1939.[3] More recent developments have been summarized in publications from this laboratory[4-6] and from that of Barach.[7] Hand in hand with the development of suitable sympathomimetic agents for aerosol use in the treatment of bronchial asthma, there has been a gradual development of nebulizing devices, culminating in the simple, unbreakable, plastic Vaponefrin nebulizer which is most commonly employed in this country and the complex "aerosolizers" of Dautrebande and his coworkers in Europe.[8]

Epinephrine, the hormone of the adrenal medulla, is the parent substance of the sympathomimetic amines. It is a secondary amine and, basically, an ethylamine derivative. Gunn[9] and, later, Graham and Gurd[10] separated those

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sympathomimetic amines which are ethylamine derivatives from a second group derived from isopropylamine (ephedrine and its congeners). All the substances under discussion at this time are ethylamines. The structural formulas of the three compounds under discussion are presented in Fig. 1. Chemically, Isuprel differs from epinephrine only in the substitution of an isopropyl radical for a methyl group in the aliphatic portion of the molecule. Neo-Synephrine is even more similar to epinephrine structurally, the only difference being the absence of the para-hydroxyl group present in epinephrine. As will be demonstrated with regard to the bronchi, and as is well known so far as pressor

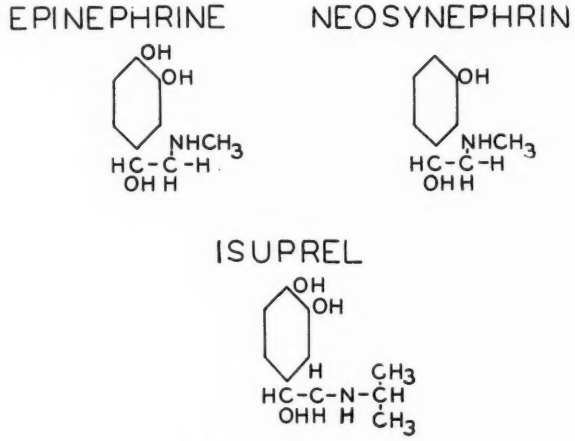

Fig. 1.—The structural formulas of epinephrine, Neo-Synephrine, and Isuprel.

activity is concerned,[9] this alteration in the aromatic portion of the molecule produces greater variations in the pharmacological properties of the compound than do changes in the aliphatic chain. Vaponefrin is chemically identical to epinephrine, but epinephrine consists solely of the levo-rotatory isomer, whereas Vaponefrin is a racemic mixture of both levo- and dextro-rotatory isomers. Since the dextro-rotatory epinephrine is less active pharmacologically than the levo-rotatory isomer, Vaponefrin may be expected to be less potent by weight than epinephrine.

METHODS

The technique of estimating the potency of bronchospasmolytic drugs by the repeated production of controlled and measured dyspnea and bronchospasm in asthmatic individuals by means of suitable bronchospastic agents (histamine, acetylcholine derivatives, pollens and other allergens) has a long and fascinating history. The methods we have employed, as well as their historical development, have been presented elsewhere.[11, 12]

In the experiments here reported, the bronchospastic agents employed were histamine diphosphate (Abbott) and acetyl-beta-methylcholine chloride (Mecholyl chloride, Merck), hereinafter referred to simply as mecholyl. The protecting ability of the therapeutic agent under examination was determined by serial observations of the reduction in vital capacity produced by repeated administration of a constant dose (predetermined as capable of producing at least 25 per

cent reduction in vital capacity) of histamine or mecholyl at varying intervals after the protecting agent was administered. The degree of protection afforded by the drug in question may be described in terms of the following equation:

$$P = \frac{C - E}{C} \times 100,$$

where P is the degree of protection in per cent, C, the control drop in vital capacity occurring after administration of the bronchospastic substance (before the protecting drug is given), and E, the drop similarly produced at any time after the protecting agent has been administered. These percentage values may then be massed into averages derived from several experiments on different subjects. Determination of such averages is necessary, for we have repeatedly encountered single protection studies, or even repeated studies in the same individual, which were greatly at variance with the average of results obtained by employing the same drugs in many experiments carried out on many individuals. This procedure facilitates the presentation of data obtained from experiments on different subjects in one curve of increased statistical probability. Each of the figures herein presented represents the average of at least four individual protection studies.

In the comparison of these agents a minor variable may appear, namely, the physical characteristics of the solution in question and of the mist obtained by nebulizing it.[13] Each of the materials commonly employed as an aerosol in the treatment of bronchial asthma is dispensed in a glycerin-water solution, the viscosity and surface tension of which have been adjusted to produce an aerosol of desirable particle size distribution. There is a certain degree of variability in the concentration of glycerin and other diluents in these mixtures, and therefore, ultimately in the particle size distribution of the aerosols produced. This will, in turn, lead to variations in the effect of the medications contained in these aerosols. This minor variation, however, is probably not of sufficient magnitude to influence the results here presented.

RESULTS

1. Epinephrine Hydrochloride 1:100.—Six inhalations of the mist produced from a solution of epinephrine hydrochloride 1:100 by hand-bulb nebulization with the Vaponefrin nebulizer provided excellent protection (75 per cent) against the bronchospastic effects of intravenous histamine. The results were immediate (five to ten minutes after administration); however, the degree of protection decreased fairly rapidly, reaching the level of 40 per cent after twenty-eight minutes. In view of the numerous sources of error inherent in any technique of clinical assay, we have proposed[11, 12] this 40 per cent level to be the minimum degree of protection which may be considered significant. By contrast, epinephrine 1:100 was less potent in counteracting the effects of intravenous mecholyl, showing an immediate protection of 56 per cent, which fell to 40 per cent at the end of eighteen minutes. These results and those presented below are presented graphically in Fig. 2 and in tabular form in Table I.

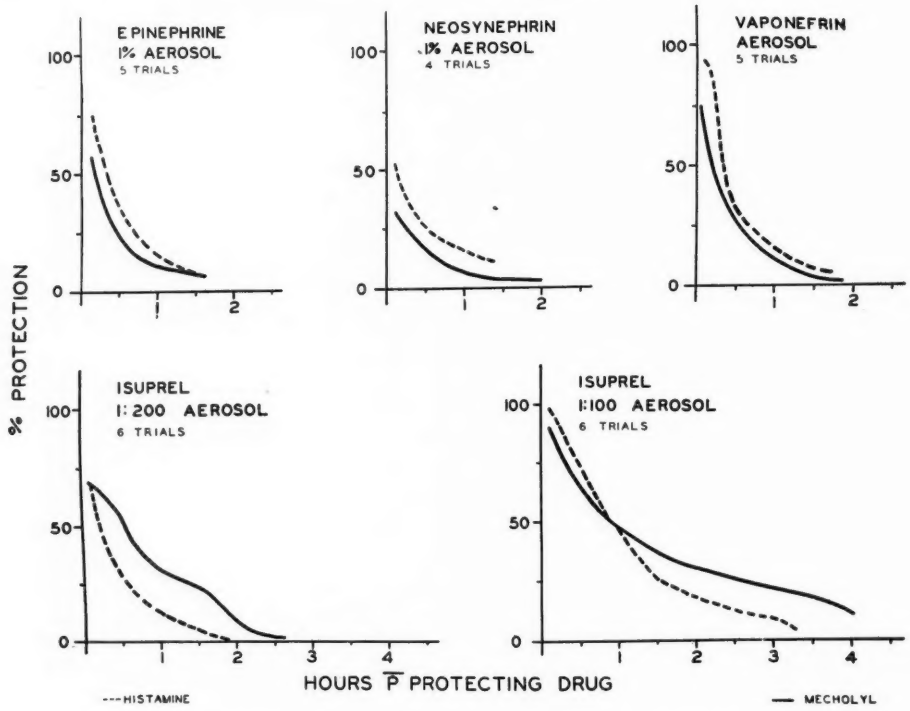

Fig. 2.—The protecting ability of various sympathomimetic amine aerosols against the bronchospastic effects of histamine and mecholyl administered intravenously.

TABLE I. THE PROTECTION AFFORDED BY VARIOUS SYMPATHOMIMETIC AMINE AEROSOLS IN PREVENTING DYSPNEA AND BRONCHOSPASM INDUCED BY INTRAVENOUS HISTAMINE AND MECHOLYL

	BRONCHOCONSTRICTING AGENT			
	HISTAMINE I.V.		MECHOLYL I.V.	
PROTECTING AEROSOL	IMMEDIATE PROTECTION (PER CENT)	DURATION OF SIGNIFICANT PROTECTION— 40% (MINUTES)	IMMEDIATE PROTECTION (PER CENT)	DURATION OF SIGNIFICANT PROTECTION— 40% (MINUTES)
Epinephrine (1:100)	75	28	56	18
Vaponefrin (2.25%)	93	27	74	18
Neo-Synephrine (1:100)	52	16	32	0
Isuprel (1:200)	70	22	69	42
Isuprel (1:100)	98	62	91	81

2. Vaponefrin.—The chemical and pharmacological properties of Vaponefrin have been described by Munch, Gattone, and Pratt.[14] In acute toxicity tests on animals, they found that, following injection, Vaponefrin was about two-thirds as toxic as epinephrine. In chronic inhalational studies on rabbits, no toxic effects were observed following inhalation of up to 4,000 inhalations of Vaponefrin. Finally, the pressor potency of Vaponefrin base was found to be about two-thirds the pressor potency of epinephrine base following intravenous injection in anesthetized cats, dogs, and monkeys. Richards, Barach, and Crom-

well[15] considered Vaponefrin clinically preferable to the official 1:100 solution of epinephrine hydrochloride. This preparation has been extensively employed by numerous investigators as a potent bronchodilator aerosol.[16-20]

Vaponefrin demonstrated greater protecting ability in these experiments than 1:100 epinephrine. Against histamine, Vaponefrin displayed essentially complete immediate protection (93 per cent), with significant protection (40 per cent or higher) which persisted for twenty-seven minutes (Fig. 2). Its protection against the effects of mecholyl-induced bronchospasm was less marked than against histamine, ranging from immediate protection of 74 per cent, with significant protection persisting for eighteen minutes. Thus Vaponefrin surpasses epinephrine 1:100 in the completeness of immediate protection against both histamine and mecholyl. Both Vaponefrin and epinephrine 1:100 protect more efficiently against histamine than against mecholyl.

3. Neo-Synephrine 1:100.—Neo-Synephrine 1:100 has often been used as a bronchodilator aerosol.[16, 19, 20] Graeser[3] found it far inferior to epinephrine in the same concentration. However, Richards, Barach, and Cromwell[15] were able to produce significant bronchodilation with Neo-Synephrine 1:100 by their continuous inhalation technique. It has a prolonged and marked local vasoconstrictor action after local application to the mucous membranes of the respiratory tract, but it is a poor bronchodilator. It may provide a more patent airway by virtue of its action as a bronchovasoconstrictor.[19, 20, 21] In these experiments (Fig. 2) its immediate protecting capacity against the effects of histamine was only 52 per cent, with significant levels being maintained for only sixteen minutes. No significant protection action against the bronchospastic effects of mecholyl could be demonstrated.

4. Isuprel.—During the early years of this decade, occasional reports from Europe mentioned an extremely potent bronchodilating agent, known as "Aleudrin."[22, 23] It was extremely efficacious in the treatment of clinical asthma and was rated superior to all other compounds tested in counteracting the dyspnea induced by aerosols of carbaminoylcholine. In animal experiments Aleudrin was described as ten times more powerful than epinephrine. This drug, under the name of Isuprel, was first introduced into the American literature in 1947 by Segal and Beakey,[24, 25] who were not aware of its chemical identity with Aleudrin until their studies were nearly completed. The pharmacological properties of Isuprel have been reported in detail by Marsh, Pelletier, and Ross[26] and by Lands, Nash, Dertinger, Granger, and McCarthy.[27]

Isuprel is ordinarily employed in a dilution of 1:200, a solution one-half as concentrated as that used with epinephrine and Neo-Synephrine, and approximately one-fifth as concentrated as Vaponefrin. This solution demonstrated 70 per cent immediate protection against the effects of histamine; significant protection was maintained for twenty-two minutes. Surprisingly, it proved to be of greater protecting value against the effects of mecholyl; 69 per cent immediate protection dropped quite slowly to 40 per cent at the end of forty-two minutes (Fig. 2). Thus, Isuprel 1:200 demonstrated more prolonged and more intense protection against the effects of mecholyl than epinephrine, Vaponefrin or Neo-Synephrine, but was inferior as a histamine antagonist to both epinephrine 1:100 and Vaponefrin.

Isuprel 1:100 demonstrated complete immediate protection (98 per cent) against the effects of both histamine and mecholyl. This protecting action gradually lessened, and dropped to 40 per cent after sixty-two minutes in the case of histamine, and after eighty-one minutes with mecholyl (Fig. 2). Isuprel 1:100 proved to be the most effective aerosol for protection against the effects of histamine and mecholyl in our laboratory. It is unfortunate that this concentrated solution is too prone to produce disturbing side effects for routine clinical use, particularly for the ambulatory patient.[24, 25]

DISCUSSION

These laboratory studies confirm our previous reports on the clinical management of bronchial asthma.[4, 5, 6, 24, 25] Both Isuprel 1:200 and Vaponefrin are effective bronchodilator aerosols with powerful, albeit short-lived bronchospasmolytic properties. Isuprel is the most powerful antagonist of acetylcholine; Vaponefrin the most potent against the effects of histamine. Clinical experience with the two preparations reveals that either of the drugs may prove more satisfactory in any individual patient, and that the comparative potency of the two preparations may vary from time to time in the same patient. Patients may become refractory to either drug but loss of sensitivity to one is not associated with fastness to the other. Both Isuprel 1:200 and Vaponefrin have valuable places in the armamentarium of the clinician treating bronchial asthma. One must determine which is the drug of choice for each individual patient at any given time by careful observation and clinical trial. Neo-Synephrine 1:100, an effective bronchovasoconstrictor with minimal antihistaminic properties, has an advantage in that refractoriness is rarely observed. It may be combined with any of the other amines to provide an effective solution for aerosolization.

SUMMARY

1. The protecting capacity of aerosols of epinephrine (1:100), Neo-Synephrine (1:100), Vaponefrin, and Isuprel (1:200 and 1:100) against the bronchospastic effects of intravenous histamine and acetyl-beta-methylcholine has been described.

2. Isuprel 1:100 was the most effective agent tested for protection against the effects of both histamine and acetyl-beta-methylcholine but was too prone to produce disturbing side reactions for routine clinical use.

3. Isuprel 1:200 demonstrated more prolonged protection against the effects of acetyl-beta-methylcholine than either 1:100 epinephrine or Vaponefrin but less immediate and prolonged protection against the effects of histamine than either 1:100 epinephrine or Vaponefrin.

4. Vaponefrin demonstrated more intense immediate protection against the effects of histamine and acetyl-beta-methylcholine than aerosols of epinephrine 1:100.

5. Neo-Synephrine 1:100 demonstrated minimal significant protection against the effects of histamine. No significant protection against the effects of mecholyl could be demonstrated.

6. The bronchospasmolytic properties of aerosols of epinephrine, Isuprel and Vaponefrin, demonstrated clinically, were confirmed in the laboratory and the relative values of these drugs as anticholinergic or antihistaminic agents were evaluated. More definitive usage of one or another of these aerosols should be predicated on the type of asthma presented by the individual patient.

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CLINICAL AND EXPERIMENTAL STUDIES WITH ORTHOXINE IN THE TREATMENT OF BRONCHIAL ASTHMA*†

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DESPITE certain disadvantages, ephedrine has continued to be one of the most effective of oral medications for the treatment of bronchial asthma. However, sympathomimetic compounds recently have been synthesized which, like ephedrine, are active bronchodilators when given by mouth, but in contrast possess relatively little pressor or central nervous system stimulating effect.[1-3] A preliminary survey of three such compounds, orthomethoxy-beta-phenyl-n-propyl-di-methylamine hydrochloride, orthomethoxy-beta-phenyl-n-propyl-methylamine hydrochloride, and orthomethoxy-beta-phenyl-isopropyl methylamine hydrochloride indicated that the last one, which has been named Orthoxine,‡ appeared to be effective in relieving asthma.[4] In view of the obvious advantages of such a compound for the treatment of bronchial asthma further studies were considered worth while.

MATERIAL AND METHODS

Orthoxine was administered orally in doses of 180 to 400 mg. and intramuscularly in doses of 200 to 250 mg. to two groups of asthmatic subjects, and on other occasions 30 mg. of ephedrine sulfate were given orally or intramuscularly. The effectiveness of both drugs and the degree of side reactions could thus be compared. The first group included twelve patients with bronchial asthma who were cooperative and had been subjected to numerous tests of vital capacity so that they were well trained. No attempt was made to classify the type of asthma, but the majority of the patients were young adults with nonseasonal attacks. Studies were carried out by methods previously described.[5, 6, 7] In brief, subjects came to the laboratory in a relatively asthma-free state and, after a period of rest and reassurance, from three to six control vital capacities were recorded on a rapidly moving drum. An evanescent asthmalike attack, with reduction in vital capacity of about 1,000 ml., was then induced by the intravenous injection of 0.01 to 0.04 mg. of histamine base or the intramuscular injection of 1 to 6 mg. of methacholine chloride. When the vital capacity returned to the resting level, Orthoxine or ephedrine sulfate was given and vital capacities again determined at intervals. Frequently there was an increase of variable degree in the vital capacity following the administration of the antiasthmatic agents. Identical doses of histamine or methacholine were then repeated at intervals of from ten to sixty minutes and any change in the vital capacity was recorded. The degree of

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protection against the reduction in vital capacity due to histamine or methacholine afforded by Orthoxine or ephedrine was computed by the following formula. In it, per cent protection is mesaured in terms of maximum decreases in vital capacity due to histamine or methacholine expressed as fractions of the preceding resting vital capacity.

$$\frac{\frac{De}{Ve} - \frac{Dt}{Vt}}{\frac{De}{Ve}} \times 100 = P \text{ (per cent protection)}$$

De = control decrease in vital capacity after histamine or methacholine.
Ve = control vital capacity before histamine or methacholine.
Dt = decrease in vital capacity after histamine or methacholine during the particular test.
Vt = vital capacity before histamine or methacholine during the particular test.

The degree of protection probably should exceed 50 per cent in order to be significant, but in the case of drugs given by mouth a lower figure may be acceptable.

Clinical studies were made in a second group composed of twenty-one patients with bronchial asthma. The antiasthmatic effect of 200 mg. doses of Orthoxine was compared with the effect of 30 mg. doses of ephedrine sulfate. In this study of the two drugs, the degree of subjective relief was noted together with the occurrence and extent of any side reactions. Five of these patients came to the laboratory with attacks of spontaneous asthma and vital capacity studies were made before and after the administration of Orthoxine.

Orthoxme was given intramuscularly in doses of 100 to 400 mg. to twenty-six subjects, the majority without bronchial asthma, and the blood pressure and pulse were recorded over a period of approximately two hours. A clinical type mercury sphygmomanometer was used for recording the blood pressure.

RESULTS

Protection Studies.—In four subjects, five protective tests against histamine-induced reductions in the vital capacity were made with doses of 250 mg. of Orthoxine intramuscularly and in three instances comparison was made with the protective effect of a 30 mg. intramuscular injection of ephedrine sulfate. The results (Table I) show that, in the doses used, Orthoxine and ephedrine sulfate afforded comparable protection against the reduction in vital capacity due to parenteral histamine. In subject A. L. (Fig. 1), for example, an intravenous injection of 0.03 mg. of histamine base was followed by a reduction of 2,017 ml. in the vital capacity and all the signs and symptoms of severe asthma. Twenty minutes later the vital capacity was still 1,003 ml. less than the resting level. Failure to return to the resting level at this time indicates an unusually severe reaction to histamine. However, ten minutes after the intramuscular injection of 250 mg. of Orthoxine, the vital capacity was only 415 ml. less than the control vital capacities determined prior to the injection of histamine. At this time and again twenty minutes later, injections of 0.03 mg. of histamine base produced reductions in vital capacity

slightly greater than the control reduction due to histamine before Orthoxine was given. However, one hour after Orthoxine administration, an identical dose of histamine caused a reduction in vital capacity of only 783 milliliters. Two hours after Orthoxine was administered there was no significant reduction in vital capacity or signs or symptoms of asthma following the histamine injection, indicating complete protection, despite a highly reactive tracheobronchial tree.

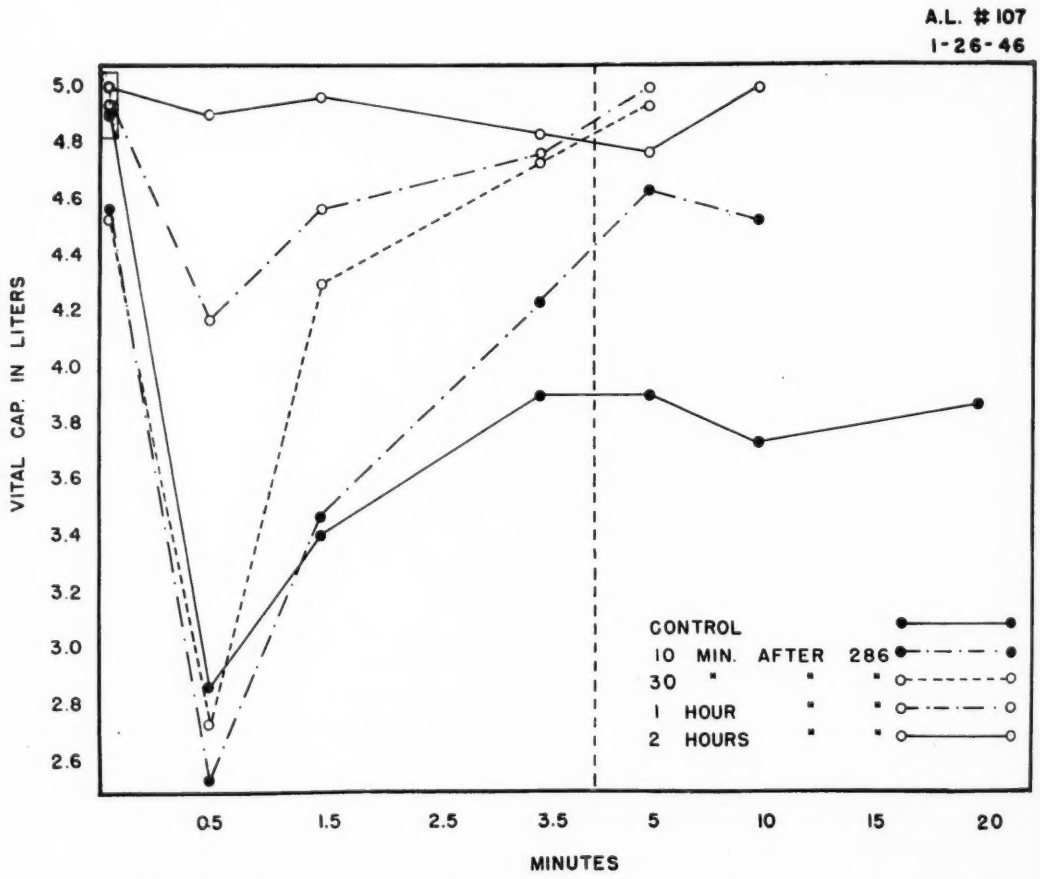

Fig. 1.—The effect of 250 mg. of Orthoxine (286) on repeated intravenous doses of 0.03 mg. of histamine base as measured by changes in the vital capacity. The shaded box on the left represents the control range of vital capacities before administration of any drug. The interrupted vertical line signifies a change in time intervals which are represented as minutes after the injections of histamine.

In ten subjects, protection tests against methacholine-induced reduction in vital capacity were made with Orthoxine in intramuscular or oral doses of 180 to 400 mg. and in five of these subjects comparison was made with 30 mg. of ephedrine sulfate similarly administered. The results (Table II) showed a variable protection ranging from 0 to 100 per cent. In some instances, the tests were concluded before a long enough period of observation had been made. The degree of protection afforded by Orthoxine was again comparable to that given by ephedrine sulfate, in the doses used in these studies.

TABLE I. PROTECTION* AFFORDED BY INTRAMUSCULAR ORTHOXINE OR EPHEDRINE SULFATE AGAINST THE MAXIMUM REDUCTION IN VITAL CAPACITY DUE TO INTRAVENOUS HISTAMINE

SUBJECT	ORTHOXINE (MG.)	EPHEDRINE SULFATE (MG.)	REDUCTION IN VITAL CAPACITY IN ML. DUE TO INTRAVENOUS HISTAMINE: BEFORE ORTHOXINE OR EPHEDRINE	TIME IN MINUTES OF REPEATED HISTAMINE INJECTIONS AFTER ORTHOXINE OR EPHEDRINE: 10	30	60	90	120	150	180
C. C.	250		826	512 (39)	323 (61)	482 (36)	293 (65)			
		30	898	846 (6)	711 (29)	648 (35)				
B. R.	250		1,150	2,000 (0)	1,422 (0)	877 (32)	700 (54)	408 (69)		
		30	2,090	1,355 (65)	440 (79)	125 (94)		125 (94)		105 (95)
A. L.	250		2,017	1,047 (44)	1,776 (5)	783 (61)	105 (95)			
J. B.	250		1,385	245 (72)*						

*Figues in parentheses represent per cent protection.

TABLE II. PROTECTION* AFFORDED BY ORTHOXINE OR EPHEDRINE SULFATE AGAINST THE MAXIMUM REDUCTION IN VITAL CAPACITY DUE TO INTRAMUSCULAR METHACHOLINE

SUBJECT	ORTHOXINE (MG.)	EPHEDRINE SULFATE (MG.)	REDUCTION IN VITAL CAPACITY IN ML. DUE TO I.M. METHACHOLINE: BEFORE ORTHOXINE OR EPHEDRINE	TIME IN MINUTES OF REPEATED METHACHOLINE INJECTIONS AFTER ORTHOXINE OR EPHEDRINE: 10	30	60	90	120
W. J.	200 p.o.		836		491 (42)	313 (67)	261 (73)	
		30 p.o.	1,253		669 (47)	763 (47)	887 (36)	867 (40)
F. W.	180 p.o.		899		366 (57)	1,463 (0)		
		30 p.o.	648		1,108 (0)	638 (0)		
J. D.	180 p.o.		1,245		899 (29)	1,223 (2)	752 (40)	1,087 (17)
		30 i.m.	1,431	220 (85)	1,023 (33)	398 (74)	115 (92)	
B. R.	250 i.m.		2,560		2,079 (16)	1,495 (38)	387 (84)	2,017 (20)
	250 i.m.		1,138	950 (25)	386 (71)	595 (56)	460 (66)	
		30 i.m.	1,076	542 (54)	335 (72)	241 (80)	157 (87)	
A. L.	250 i.m.		1,724	606 (67)	470 (75)			
		30 i.m.	1,723	826 (47)	470 (71)	501 (71)	1,087 (45)	
M. M.	250 i.m.		544		251 (56)	0 (100)		
S. M.	200 p.o.		669		574 (10)	449 (25)	513 (20)	
J. M.	180 p.o.		658		888 (0)	533 (19)		
J. DeL.	400 p.o.		1,077		896 (18)	1,035 (4)	502 (56)	816 (28)
H. W.	200 i.m.		703		1,515 (22)	1,557 (26)	1,171 (43)	

*Figures in parentheses represent per cent protection.

Clinical Studies.—Twenty-one patients with mild spontaneous asthma, controlled by oral antiasthmatic drugs, took 200 mg. Orthoxine by mouth three times daily and the clinical response and side reactions were noted. After a period of three to four weeks, 30 mg. doses of ephedrine sulfate were substituted and the clinical results again recorded. Some of these patients were deliberately chosen because they had complained of untoward side reactions after ephedrine in the past. In every case it was reported that Orthoxine furnished as effective a relief of asthma as ephedrine sulfate and in six cases Orthoxine was reported to be more effective. Of five cases reporting "jitteriness" after ephedrine no such complaint was elicited after Orthoxine and in two other cases "jitteriness" was much less pronounced after Orthoxine than after ephedrine sulfate. Two patients receiving Orthoxine reported slight drowsiness and in one case there was a lightheaded feeling, more pronounced than after ephedrine.

Five patients came to the laboratory with attacks of spontaneous asthma and, after control vital capacities were recorded, they were given 200 mg. of Orthoxine orally. Maximum increases in vital capacity of 115 to 1,108 ml. (Table III) occurred following the administration of Orthoxine.

TABLE III. CHANGES IN VITAL CAPACITY AFTER ORTHOXINE IN PATIENTS WITH SPONTANEOUS ASTHMA

		VITAL CAPACITY DETERMINATIONS IN ML. IN SPONTANEOUS ASTHMA							
			AFTER ORTHOXINE						
SUBJECT	ORTHOXINE BY MOUTH (MG.)	BEFORE ORTHOXINE	10 MIN.	30 MIN.	1 HOUR	1½ HOURS	2 HOURS	2½ HOURS	MAXIMUM INCREASE (ML.)
F. W.	200	2,016	2,351	2,549	2,498	2,518			533
F. G.	200	1,745		1,975	2,226	2,299	2,769	2,382	1,024
J. DeL.	200	2,790		2,633	3,501	3,793	3,898	3,898	1,108
M. M.	200	1,724		1,839	1,327	1,818			115
J. A.	250	2,581	2,633	3,009	2,654				428

In twenty-four subjects, the majority free from asthma, given 100 to 200 mg. Orthoxine intramuscularly, only two showed an elevation of systolic pressure of more than 15, or of the diastolic pressure of more than 10 mm. of mercury. In a few cases the blood pressure appeared to fall after the drug was administered. Pulse rate was increased by more than ten beats per minute in only one instance. A more forceful, but not more rapid, heartbeat was noted in two cases. Three subjects with moderate essential hypertension were given 400 mg. of Orthoxine intramuscularly with a subsequent rise in systolic pressure of 30 to 36 and in the diastolic pressure of 8 to 20 mm. of mercury.

DISCUSSION

The problem of evaluating antiasthmatic drugs under any circumstances is a real one, but when these agents are given orally comparison is even more difficult. If paroxysms of asthma are mild, many agents appear to be effective in bringing about relief, but when attacks are more severe, no oral medication

affords notable improvement. This difficulty has in part been met by assaying the various antiasthmatic agents by the degree of protection afforded against the reduction in vital capacity and asthmalike attacks induced by the parenteral administration of histamine and methacholine. Here again, however, protection tests performed with oral drugs frequently are not as clear-cut as tests made with agents that are given parenterally. In the doses used in our studies, Orthoxine and ephedrine sulfate furnished variable but comparable protection against the asthmalike attacks induced by parenterally administered histamine and methacholine. The results of these tests were confirmed by clinical studies of the two drugs in which comparable relief was obtained with both agents in cases of spontaneous asthma. Thus, the validity of the first method of study is supported. However, side reactions were much less frequent after Orthoxine than after ephedrine sulfate. There was very little pressor effect and central nervous system stimulation was infrequent and minimal. In fact, in two or three cases, it seemed that a mild sedative effect was secured. This absence of central nervous stimulating effect is important because it obviates the necessity of prescribing barbiturates along with the bronchodilating agent. As indicated in a recent paper, the barbiturates may have a deleterious effect in patients with bronchial asthma.[8] Apparently the drug may be safely administered to asthmatic patients with essential hypertension. The number of cases studies were too few to determine exactly the time of onset and duration of action of Orthoxine but in these respects the drug appears to be similar to ephedrine sulfate.

SUMMARY

1. Clinical and experimental studies of Orthoxine and ephedrine sulfate were made in two groups of patients with bronchial asthma.

2. Experiments showed that Orthoxine, in doses of about 200 mg., was comparable to ephedrine sulfate, in 30 mg. doses, in protecting the asthmatic subject against the reduction in vital capacity and asthmalike attacks due to parenteral histamine or methacholine.

3. Clinical studies with the two drugs indicated that in the doses used they were equally effective in relieving mild cases of asthma. However, side reactions were much less frequent after Orthoxine and there was little or no pressor or central nervous stimulating effect.

4. It appears that Orthoxine has a definite place in the management of bronchial asthma because it is an effective bronchodilator drug that may be given orally and it is followed by relatively few undesirable side reactions.

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DISCUSSION

DR. IRVING SCHILLER, Boston, Mass.—An oral preparation that gives promise of having ephedrine-like qualities without unpleasant pressor and central nervous system side reactions of ephedrine is obviously of great interest to us.

The protective studies that Dr. Curry and his associates carried out indicate the effectiveness of Orthoxine as a bronchodilator. There is just enough difference, however, between the asthmalike attacks induced by parenteral injections of histamine or methacholine and those induced by allergenic extracts when given by inhalation, so that we would like to see these experiments repeated using allergens in sensitive individuals.

Last spring we began using Orthoxine in the Allergy Clinic at the Massachusetts Memorial Hospitals and at present we have data on a group of forty-six asthmatic subjects.

There was no special selection of cases and except for status asthmaticus, the drug was used without regard for the severity of the asthma.

Recognizing the tendency of patients to overestimate the efficacy of a new drug when used for the first time and also, as Dr. Curry points out, the hazards of evaluating oral medications, we have, nevertheless, gathered certain impressions about Orthoxine.

Using an oral dose of the drug somewhat short of that employed by Dr. Curry and associates (and this may perhaps explain some of the difference in our results), we found that the drug gave satisfactory relief in thirty-two of the forty-six or 70 per cent of the cases. Of this group there were five patients or 11 per cent in which the drug was very effective and in these cases was even more effective than ephedrine. In 25 per cent of the total number of cases Orthoxine was a flat failure. This was rather striking and disappointing. Taking the group of patients as a whole, ephedrine on a comparative basis seemed to be superior. As with Dr. Curry's patients the side effects were unimportant.

On the basis of these findings and Dr. Curry's observations, we feel that there is a definite place for Orthoxine and that it should make a valuable addition to the list of antiasthmatic drugs.

THE INHALATION OF 1-(3′,4′-DIHYDROXYPHENYL)-2-ISOPROPYLAMINOETHANOL (NORISODRINE SULFATE DUST)*

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THERE have been many favorable reports on the use of Norisodrine sulfate as a bronchodilator. This drug has been known in the European literature as "Aleudrin" and chemically identified as 1-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol. Its chief clinical use has been in the symptomatic treatment of asthmatic conditions. A considerable number of animal and human experiments have been carried out in relation to the properties of this drug. There is general agreement in the literature that this drug possesses the following important characteristics: (1) that it is more effective than epinephrine in overcoming bronchiospasm induced experimentally; (2) that it may cause vasodilation with a consequent fall in blood pressure; (3) that it may cause an increase in the coronary output; (4) that it may cause tachycardia, dizziness, and nausea if given in large doses subcutaneously; (5) that there is very little evidence of addiction; (6) that it has proved effective in asthmatic patients who could not obtain relief with epinephrine, theophylline, or ephedrine; (7) that there is no evidence of "fastness" for this drug; (8) that the administration by inhalation appears to be the route of choice; (9) that it is effective when given orally, sublingually, subcutaneously, and by inhalation; and (10) that when given by inhalation, the side-reactions are infrequent, minimal, and transitory.

Konzett[1] reported that Norisodrine sulfate was ten times more effective than epinephrine in abolishing bronchoconstriction induced in dogs with pilocarpine. Dautrebande,[3] using the aerosol technique in the treatment of bronchial asthma, stated that up to five or ten inspirations of a 1:1,000 solution of Norisodrine produces sustained bronchiodilation without alarming side-effects. Stolzenberger-Seidel,[5] using a 1:100 solution of Norisodrine reported very favorable results in 100 cases. He stated that full relief from the asthmatic paroxysm was obtained within two to five minutes. He pointed out that where this drug has been used for one year or longer there has been no evidence of diminution in effectiveness. Quitschal[6] reported the successful treatment of 148 asthmoidal conditions arising from chronic bronchitis and emphysema with Norisodrine. 1 per cent solution of the drug was inhaled in his series of cases. In many instances liquefaction and expectoration were facilitated by the use of this drug. According to this author there was a remarkable increase of the vital capacity in patients with emphysema. The technique used in this study was to have the patient inhale 1 per cent Norisodrine solution three times a day, taking fifteen inspirations each time. No addiction to the drug was observed. In this study only five of 148 patients reported cardiac palpitation which disappeared five minutes following inhalation.

Segal and Beakey,[7] in a study on eighty-two patients, reported very favorable results using Norisodrine by aerosolization with oxygen, subcutaneously,

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and orally. Patients receiving aerosol therapy were given 1 c.c. of a 1:100 solution every three hours; those receiving it subcutaneously were given 0.20 to 0.33 c.c. of a 1:1,000 solution every three to six hours. These authors stated that the side-reactions were minimal with the aerosol technique, but can be serious when the drug is given subcutaneously. It was pointed out that more than 0.5 mg. of the drug should never be given subcutaneously. A study of the blood pressure and pulse response in five normal subjects was carried out. When these subjects received 1 c.c. of the 1:100 solution by aerosol, the average rise of the systolic pressure was 13 mm. of mercury; the average increase in pulse pressure was 16 mm. of mercury. When 0.33 c.c. of a 1:1,000 solution was given subcutaneously, the average increase in systolic blood pressure was 22 mm. of mercury with an average increase in the pulse pressure of 39 mm. of mercury. With the aerosol, the average increase in pulse rate was 18 beats per minute, whereas with the subcutaneous injection the average pulse rate increased 50 beats per minute. It was pointed out that the greater the degree of bronchospasm, the greater the degree of improvement in the vital capacity. Eleven patients who did not respond to epinephrine, improved satisfactorily with Norisodrine medication.

Previous reports[9, 10, 11] have indicated that the inhalation of penicillin in the form of a dust is a very practical and efficient means of introducing a drug into the respiratory tract. The inhalation of penicillin as a dust, it was pointed out, has a number of mechanical and therapeutic advantages. They are: simplicity of equipment and administration, maximum concentration of drug per unit area within the respiratory tract, slow absorption into the systemic circulation, no dilution of drug is necessary, the apparatus is pocket size and may be kept for instantaneous use at all times, and no oxygen or nebulizer is required to aerosolize the medicament. It was believed that these advantages could apply to Norisodrine if used in dust form and at the same time widen the application of a drug with such useful clinical properties.

Apparatus.—This device consists of a molded plastic discharge chamber with a detachable mouth piece. The Norisodrine dust is contained in a small plastic cartridge, the bottom of which is fitted with a fine mesh wire screen through which the Norisodrine dust is released. The upper rim of the cartridge exhibits two small phlanges which fit into a groove and allow locking of the cartridge in position in the discharge chamber. The distal end of the discharge chamber is formed into a curved-tube runway containing an aluminum ball. On inhalation the aluminum ball is rapidly drawn up the runway until it strikes the cartridge containing the Norisodrine dust; the impact causes a release of a small amount of the Norisodrine dust into the discharge chamber. The upper end of the runway is grooved so that the air to be inspired can bypass the aluminum ball after it strikes the cartridge. The inspired air, as it bypasses the ball, carries the released Norisodrine dust into the respiratory passages. Thus, with each respiration a small but uniform amount of dust enters the respiratory passages.

Procedure.—In view of some mild, but definite, untoward reactions observed with the use of Norisodrine sulfate in aqueous solution, the response of six normal subjects to the inhalation of this drug in dust form was studied. Each

subject inhaled the amount of dust (3 to 5 mgs.) released during one normal inspiration. Pulse rate, blood pressure (readings taken immediately and at two-minute intervals) and subjective findings were recorded following inhalation. The maximum changes were recorded. Table I depicts the nature of these changes and is based on the average of five individual trials for each subject.

TABLE I. THE RESPONSE OF PULSE AND BLOOD PRESSURE TO A SINGLE INHALATION OF NORISODRINE DUST IN SIX NORMAL SUBJECTS

	PULSE*		BLOOD PRESSURE*		
SUBJECT	BEFORE INHALATION	AFTER INHALATION	BEFORE INHALATION	AFTER INHALATION	SYMPTOMS
1.	84	86	110/70	112/70	None
2.	80	78	114/76	110/74	None
3.	74	74	120/80	118/80	None
4.	82	84	112/76	112/76	None
5.	72	76	106/70	104/72	None
6.	76	80	122/74	112/74	None

*These values represent the averages obtained from five separate experiments in which the same six subjects were used.

A group of twenty-four asthmatic patients with symptoms ranging from three to twenty-eight years were studied. These patients were apparently not satisfactorily controlled with the usual drugs such as epinephrine (either by injection or by inhalation), aminophylline, iodides, ephedrine, Pyribenzamine or Benadryl. Seven were classified as bronchial asthma with bronchitis, and seventeen as bronchial asthma of the allergic type. All discontinued their previous medication and were given a test dose of Norisodrine dust to determine the presence of any unusual sensitivity or untoward reactions. This dose consisted of the amount of drug released (3 to 5 mgs.) by one inspiration. If no unusual reactions were noted, the patient was instructed to take one inhalation of the Norisodrine dust* during an impending attack of asthma. This was to be repeated within one-half to one hour as necessary.

Results.—It soon became apparent that on the basis of the clinical response to the inhalation of Norisodrine dust, that the patients fell into two basic groups. One group could be completely and satisfactorily controlled by the exclusive use of the Norisodrine dust. The second group could only be controlled by Norisodrine when either aminophylline and iodides and/or an antihistaminic drug were being used daily. In the latter group it would appear as if the "threshold" of bronchospasm was lowered by the use of this additional medication, thus making Norisodrine more effective in controlling the asthmatic paroxysm. It should be pointed out, however, that these same drugs did not prevent the occurrence of asthmatic attacks but rather made it possible for these paroxysms to yield to the Norisodrine. The response to the inhalation of Norisodrine dust was evaluated in terms of how completely impending asthmatic attacks were aborted or to what extent the actual attack was dissolved. Sixteen patients were controlled by the inhalation of the Norisodrine dust alone. Seven of these had an associated bronchitis and were given penicillin dust inhalation, subsequently, although the asthmatic paroxysms were previously controlled with Norisodrine alone. The penicillin dust therapy in this type of case greatly reduced the

*The Norisodrine dust was processed and furnished through the courtesy of The Abbott Laboratories, North Chicago, Ill.

requirements for the Norisodrine. Eight patients were best controlled with aminophylline and iodides and/or an anti-histamine in addition to the Norisodrine. These patients received the aminophylline orally daily. In one instance the patient could not be controlled with Norisodrine plus additional medication, but this patient did not respond to epinephrine either.*

Of the eight patients requiring medication in addition to Norisodrine, one patient did not respond to Norisodrine at all, four gave a good response, and three responded satisfactorily. The results in these patients requiring additional medication might have been anticipated since they did not respond to Norisodrine alone. It will be noted that in those instances where no additional therapy was required the response to Norisodrine was satisfactory in all instances. Table I would indicate that the inhalation of Norisodrine dust is a relatively safe procedure. In normal subjects the inhalation of a single dose did not appear to influence the pulse rate or the blood pressure. No discomforting symptoms were reported by this group. Four asthmatic patients reported dizziness and/or palpitation after inhalation. These reactions were not alarming and disappeared in all instances within ten minutes. The blood pressure in these four patients showed a drop in systolic pressure ranging from 3 to 20 mm. of mercury. In this group the pulse rate showed an increase ranging from 4 to 12 beats per minute. There were no reactions in the remaining twenty patients. The changes in pulse rate and in blood pressure were negligible in most instances. Patient number one was treated while in status asthmaticus. She required a considerable amount of Norisodrine to maintain comfort. Since she tolerated the drug exceptionally well she was permitted to inhale the Norisodrine dust freely. She would consume as much as 100 mgs. of the drug daily without any untoward reactions. None of the patients, including the latter, have shown any tendency of fastness toward this drug so far. This group of patients have been using Norisodrine dust for the past nine months.

COMMENT

On the basis of the clinical results obtained with the inhalation of Norisodrine dust, either alone or in addition to other medication, it would appear that this drug has a definite place in the symptomatic treatment of asthma. It should also be useful in many instances of bronchospasm of nonasthmatic origin. It can apparently be inhaled in dust form with a wide margin of safety. Using it as a dust makes it simple for patients to inhale it. One might speculate as to why Norisodrine in 100 per cent concentration does not produce greater side-reactions. It is conceivable that since this drug is in solid form it remains in the tissues locally for a long time before complete absorption takes place. Yet, a certain amount must be absorbed readily since the clinical response occurs within a few minutes.

It is apparent that in some instances Norisodrine dust cannot be used satisfactorily to the exclusion of medication like aminophylline, iodides, and antihistaminics. The combination of drugs, however, appears to be effective where each drug by itself is ineffective. Aminophylline, iodides, and antihistaminics very likely lower the bronchospasm "threshold" and bring it within effective range for Norisodrine medication. It is well-known that in many instances epinephrine cannot be used to the exclusion of other medication and at times

*This patient appeared to be resistant to all forms of therapy. Her attacks would persist for three to five days and then stop spontaneously.

it is completely ineffective regardless of what combination of drugs are used. In asthma with bronchitis, the combination of penicillin dust and Norisodrine dust therapy appears to be very effective. These patients responded satisfactorily and eventually had to resort to very little of the Norisodrine. Norisodrine in dust form appears to be a safe drug when inhaled. It apparently can be given in large doses in some instances without any disagreeable reactions.*

SUMMARY

1. Twenty-four patients with bronchial asthma were treated by the inhalation of Norisodrine dust.

2. Nineteen responded satisfactorily and were completely under control with this form of therapy. Four showed a good response whereas one patient was not influenced at all.

3. Sixteen patients were controlled by the inhalation of the Norisodrine dust only, eight required Norisodrine plus aminophylline and iodides, and/or an antihistaminic.

4. The inhalation of penicillin dust in asthmatic patients with an associated bronchitis reduced the requirements of Norisodrine.

5. It would appear that the inhalation of Norisodrine sulfate as a dust is a safe procedure since no serious side-reactions were noted. Palpitation and/or dizziness were noted only in four of thirty subjects. These effects were transitory and disappeared within ten minutes.

6. There has been no diminution in its effect with the continued use of this drug.

7. The inhalation of Norisodrine as a dust permits the use of a device which is simple to use, may be carried at all times, and is readily available for administration in cases of impending asthmatic paroxysms.

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*In some instances where the patient disregards the prescribed dose, uncomfortable palpitation may ensue.

COLLAGEN DISEASE: ITS RELATION TO HYPERSENSITIVENESS*†

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AN INCREASED interest has been aroused recently in a subject which is not altogether new, namely, collagen disease. This involves a group of clinical conditions in which are seen various stages of connective tissue changes. Since connective tissue is found so abundantly in all arteries, arterioles and various other organs in the body, it follows that the manifestations of disease resulting from connective tissue involvement will also be widespread and varied. It is for this reason that collagen disease has also been referred to as diffuse vascular disease, arteritis, or mesenchymal disease. This includes serum disease, lupus erythematosus disseminatus, the Libman-Sachs syndrome, scleroderma, rheumatic fever, chronic rheumatoid arthritis, periarteritis nodosa, dermatomyositis, nephrosclerosis, sclerema neonatorum, and thromboangiitis obliterans. There is no evidence that these disorders have a common pathogenesis. And yet, there is sufficient clinical and experimental data to suggest that in at least some of these conditions, hypersensitiveness may play an important role. We shall present in this paper a summary of case reports or the clinical and pathologic features of each of these diseases together with a discussion of their relation to hypersensitiveness.

Literature.—Menzer,[1] in 1902, was the first to point out the possibility that rheumatic fever may be an allergic manifestation to the streptococcus. This was followed some years later by the reports of experimental work in this field by Swift[2, 3, 4] and Rich.[5-8] As early as 1923, Gerlach[9] pointed out the characteristic presence of increased connective tissue in hypersensitive phenomena. In 1929, Klinge[10, 11] injected horse serum in the joints of sensitized rabbits and produced both a necrotizing arthritis and collagen degeneration. Matsui[12] related scleroderma to collagen disease in 1924. Jaeger,[13] in 1932, suggested the possibility of an allergic background for rheumatic fever, periarteritis nodosa, and thromboangiitis obliterans. Matsugi and Ya-Shu,[14] in 1938, added scleroderma to this group. In 1935 and later, Klemperer, Baehr, and associates[15, 16, 17] wrote extensively on the subject and applied the concept of collagen diseases to cover all of these conditions, emphasizing the fact that while fibrinoid degeneration of collagen is the pathologic lesion common to all these conditions, their pathogenesis is nevertheless not the same. Clark and Kaplan,[18] in 1937, reported a case of serum disease with periarteritis nodosa. Lederer and Rosenblatt[19] reported, in 1942, arterial lesions as seen in an autopsy of a patient who had received sulfonamides. It was Gruber[20] who suggested, in 1925, the allergic basis for periarteritis nodosa because of its association with urticaria, eosinophilia, asthma, and its artificial production in animals. Masugi and associates[21, 22] produced periarteritis nodosa in sensitized animals by the intravenous injection of egg white.

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Anatomy and Physiology.—In order to understand the nature of collagen disease, it is necessary to know something about the anatomy and physiology of the connective tissue system. This system is composed of cellular elements, fibrils (white and elastic), and a homogeneous ground substance which forms the cement. The cellular element consists of fibroblasts, eosinophiles, plasma cells, pigment cells, undifferentiated cells, and fat. The white or collagenous fibers are the most characteristic constituents of connective tissue. When boiled down with water, they yield a colloidal solution of animal glue or gelatin whence the name collagen. The cement is a diffuse amorphous substance which holds the collagen and elastic fibers together. Chemically, it is an albuminoid, colloidal protein which on boiling with water gives gelatin. A glance at a section of an artery indicates how abundantly collagen is found throughout its wall. Thus, collagen separates the intima from the internal elastic membrane; it is found equally well distributed throughout the media and the adventitia. In addition, connective tissue is widely distributed in the subcutaneous tissue, serous membranes, and throughout the various organs of the body. The function of the connective tissue system is to give support to other tissues, to regulate water and salt balance, to aid in the transfer of metabolites, and to act as a depot for food storage.

Pathology.—When invaded or attacked by noxious agents, connective tissue shows enormous powers of regeneration. Sometimes this property is well localized and spontaneous, as in the case of keloid. At other times it is widespread and diffuse, involving many organs and being brought about even by minimal stimulation. The pathologic changes include many stages, all of which may be in evidence in various sections. These changes are: swelling, enlargement of the fibrils, and proliferation and degeneration of the cellular element. The cells may indicate an acute, a chronic, or an acute and chronic process. In an acute disease, such as rheumatic fever, the cellular reaction predominates so that there is a collection of large cells (Aschoff bodies) which is a reflection of the active process. As the acute process and necrosis subside, the cellular reaction becomes less evident, and is replaced by hyalinization and fibrosis. The fibrils become fragmented, refractile, and simulate the appearance of fibrin which is matted together and takes certain characteristic staining qualities, so that this is referred to as fibrinoid degeneration of collagen.

While the lesions of degeneration are morphologically similar, nevertheless in some instances they involve only blood vessels while in other conditions, connective tissue elsewhere. For example, fibrinoid degeneration is characteristic of rheumatic fever, lupus erythematosus, and scleroderma. However, one does not see the glomerular lesions of lupus erythematosus and scleroderma in rheumatic fever. Nor are the Aschoff bodies, so characteristic of rheumatic fever, seen in lupus erythematosus and scleroderma.

Pathogenesis.—Fibrinoid degeneration may develop as a result of many causes: injury by toxic metabolites, toxicity of, or allergy to drugs, shock, and endocrine imbalance (Selye reaction), foreign protein injection, other allergic factors, and, finally, the aging process. Selye has been able to show experimentally that animals respond to shock (adaptation syndrome) by developing

degenerative processes which result in arteriosclerosis and collagen degeneration. Pathologic changes with collagen deposit, which represent the end result in some of these diseases (lupus erythematosus disseminatus), are often similar to the end result seen normally in an arteriosclerotic blood vessel. We shall detail later the present available experimental work on the role of hypersensitiveness in this connection. It indicates the similarity between the pathologic changes observed in the experimental production of fibrinoid degeneration of collagen in anaphylaxis and clinical allergy on the one hand, and collagen disease on the other.

SERUM DISEASE

Serum disease occurs in a large percentage of the population following the injection for the first time of a foreign serum. The symptoms of fever, urticaria, and arthralgia (which are common also to drug allergies and rheumatic fever) have been designated as "the serum disease pattern" and become manifested after an incubation period. While the condition is usually reversible, occasionally it may display more permanent and severe visceral changes, such as periarteritis nodosa, carditis, etc.; changes in connective tissue which are characterized by fibrinoid degeneration of collagen. This has been amply demonstrated at post-mortem examination of patients with pneumonia who received serum therapy with or without sulfonamides. These patients developed symptoms of serum sickness as a result of sensitivity to serum or to sulfonamides. Typical lesions of periarteritis nodosa with collagen degeneration were found in these instances. The pathologic changes observed in serum sickness or in fatal sulfonamide and other drug reactions in man are similar to those found in spontaneous periarteritis nodosa. It would therefore appear that in at least some cases of hypersensitiveness of the serum disease pattern there are irreversible changes indicative of collagen disease.

LUPUS ERYTHEMATOSUS DISSEMINATUS

This is a constitutional, usually fatal, disease which occurs mostly in women and is manifest by long-continued fever, weakness, arthralgia, leucopenia, abdominal pain, pleurisy, and occasionally by "butterfly" erythematous lesions of the face. Other findings include pericarditis, endocarditis, anemia, nephritis, retinal changes, adenopathy, splenomegaly, and hepatomegaly. In its acute form there may be purpuric lesions or erythema multiforme. The differential diagnosis should include active endocarditis, typhoid fever, and rheumatic fever.

Pathologic examination shows fibrinoid degeneration of collagen in the wall of the smaller arteries. There is endothelial and intimal proliferation with necrosis and occasional thrombus formation. These changes are found diffused throughout the blood vessels of the body, but especially in the skin, the serous membranes, and the renal glomeruli. All varying stages of lesions may be present in the same patient but in different arteries and organs, ranging from acute cellular infiltration and swelling of the fibrils to necrosis, hyalinization, and fibrinoid degeneration. When the connective tissue of serous membranes like the pericardium, endocardium, and pleura is involved, there occurs clinical evidence of local sterile inflammation giving rise to pericarditis and pleurisy,

the so-called Libman-Sachs syndrome. Kidney sections may show various stages of glomerular degeneration, hyalinization, "wire loop arrangement," thickening of the basement membrane, and collagen degeneration. Considerable perivascular sclerosis is evident in the spleen. These microscopic findings are of diagnostic value only when coupled with the clinical picture.

Little is known about the exact etiology of lupus. The possibility that it may occur, at least in some instances, as a manifestation of hypersensitiveness to foreign proteins is indicated by a report of an 18-year-old girl who developed lupus erythematosus one week following the administration of antitetanic serum. Stokes[23, 24] suggests that in other instances the disease may be an *id* reaction, a form of sensitization to bacterial infection in the hair follicles. Sensitization in lupus erythematosus may be aided by sunlight exposure (physical allergy), infection, shock, and emotional crises.

There is a clinical and pathologic relationship between lupus erythematosus, dermatomyositis, and scleroderma. Raynaud's disease, as well as vascular, visceral lesions, subcutaneous calcification, and pigmentation of the exposed surfaces, may accompany all three conditions.

CASE REPORT

H. A. C., a white male, aged 52, was admitted to the United States Veterans Hospital at Aspinwall, Pa., on Aug. 26, 1947. He first noted exertional dyspnea three years previously. This became progressively worse and orthopnea and ankle edema developed. For two years he had a chronic productive cough with increasing malaise, weakness, fatigue, headache, anorexia, nocturia, and a weight loss of 25 pounds. Migratory joint pains appeared. There was a history of paroxysmal asthmatic attacks. No family history of allergy was recorded. He had had scarlet fever.

Physical examination revealed a poorly nourished white man. There was long-continued low-grade fever. The pulse rate was 90, the blood pressure 200/125 millimeters. A scarred, scaly, erythematous, indurated dermatitis of long standing involved the chest, arms, and dorsal surface of the forearms. Scattered râles were present at both bases. The heart and liver were enlarged. Many premature beats were present. The veins of the neck were distended. Purpuric spots appeared late in the disease.

Positive laboratory findings were as follows: heavy trace of albumin, many red blood cells, and granular casts in the urine; red blood cells, 2.5 million, with normal white blood cell count and volume index; low serum proteins with albumin-globulin ratio of 1:1; roentgenogram showed normal lung fields with numerous hilar calcifications; the heart was enlarged in all diameters with elongation and tortuosity of the aorta; electrocardiographic evidence of cardiac damage was present.

The patient's condition continued a downhill course so that six weeks after admission he became drowsy, comitose, and died in congestive heart failure on Oct. 10, 1947.

The following is a summary of the positive necropsy findings.

General.—There was a crusted, scaly skin over both external ears and ala nasae, with tannish pigmentation, and some pigmented scarred areas on the face in front of the right ear, and on the left side of the upper lip. Multiple petechiae were present on the chest, abdomen, and thighs. There were a number of grayish-white, poorly-circumscribed scaly lesions 5 to 15 mm. in diameter on the right forearm. Considerable pigmentation was associated with these lesions.

Lungs.—The left lung weighed 1,000 grams. The apex was puckered and showed irregular yellowish-pink subpleural scars, and seemed firm to palpation. The lower half of the left lower lobe was also firm, and reddish purple. There were several matchhead-sized nodules on the diaphragmatic surface. The right lung weighed 950 grams. There was scarring of the apex. The lower lobe was voluminous and firm.

Heart.—The heart was large, weighing 550 grams. The pericardial cavity was obliterated with fibrinous adhesions. There was some thickening of the anterior mitral leaflet and the chorda tendinae. There was a pinhead-sized nodule near the free end of the valve. The valve ring was dilated. The aortic valves were calcific.

Abdomen.—At the junction of the lower and middle third of the esophagus were two areas of ulceration. The ulcers extended into the muscularis. The remainder of the bowel was normal. There was a fine pitted nodularity of the liver. The cut surface was firm, granular, and dark brown. Small thrombosed vessels were noted in the parenchyma of the pancreas, and also multiple greenish-white and yellowish areas of necrosis with a sharply defined red margin. There were multiple areas of fibrosis in the spleen. The trabeculae were prominent. There was a finely granular cortex in both kidneys.

Microscopic examination showed the following positive findings:

Brain.—Calcification of small arteries were noted at the junction of the interna and media. There was hyaline thickening of the small arteries in other locations, especially in the substania nigra.

Lungs.—There were scattered areas of bronchopneumonic change in both lungs and areas showing predominantly congestive change with fibrinous and hemorrhagic exudate.

Heart.—The coronary arteries showed medial thickening and hyaline degeneration.

Aorta.—There was evidence only of calcific and atherosclerotic change.

Esophagus.—Section taken through the ulcerated zone showed the break in epithelium and typical lesions of acute infection. There was perivascular infiltration of lymphocytes in the adjacent submucosa and two small arteries displayed fibrinoid necrosis of the media.

Liver.—There was some increase in fibrinous tissue, some central degenerative change, and dilatation of the sinusoids which contained red cells.

Pancreas.—Throughout the parenchyma were large and small areas of necrosis. Some were hemorrhagic and others showed early fibrinous organization and appeared to represent zones of infarction. The vessels showed necrotizing lesions of the intima and media in a variety of stages. Some vessels had recent thrombi while others showed intimal thickening and old organizing thrombosis. The lumina of some vessels were filled with fibrinoid masses extending to the media.

Spleen.—There was marked hyaline thickening of the vessel walls and adventitia.

Kidney.—The glomeruli showed a variety of changes. Some were completely hyalinized and others showed acidophilic or fibrinoid degeneration of several capillary loops, associated with thrombosis or rarely hemorrhage. The affected loops were bloodless and the remainder often showed thickening of the basement membrane yielding the "wire loop" appearance. There were occasional adhesions of the glomerular tuft to the capsule, and epithelial proliferation. The arterioles and small arteries showed fibrinoid necroses and occasionally hemorrhage into the vessel wall. There was considerable endothelial hyperplasia in the small arteries with a pale staining fibrous thickening of the intima. Some vessels showed organizing thrombus (Figs. 1 and 2).

The pertinent anatomical diagnosis was: lupus erythematosus, disseminated; necrotizing and proliferative arteritis of the kidneys and pancreas; endarteritis of the kidneys and pancreas; hemorrhagic and ischemic infarcts of the pancreas; congestive heart failure; acute bronchopneumonia; petechiae in the skin; obsolete pulmonary tuberculosis; acute ulceration of the esophagus.

Notanda.—Autopsy disclosed very striking lesions representing many stages of arterial degeneration in the pancreas and kidneys. Collagen necrosis of arterial walls was a common finding. The renal glomeruli disclosed numerous "wire-loop" thickenings of the capillary basement membrane such as is often associated with disseminated lupus erythematosus. Death was the end result of congestive heart failure.

LIBMAN-SACHS SYNDROME

This disease,[25, 26] as indicated above, may occur as part of lupus erythematosus disseminatus. It is characterized by long-continued fever, white-centered

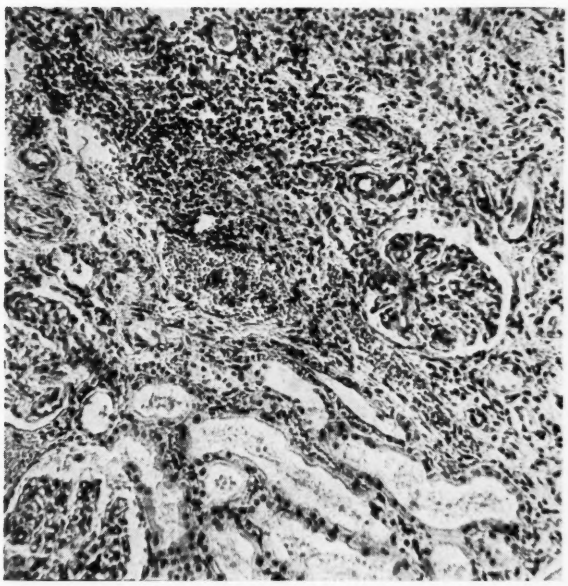

Fig. 1.—Lupus erythematosus disseminatus. Section of kidney (low power). Section shows intense, monocytic, perivascular, cellular reaction. There is thickening of the basement membrane. The capsular space is reduced. Glomerular changes are evident.

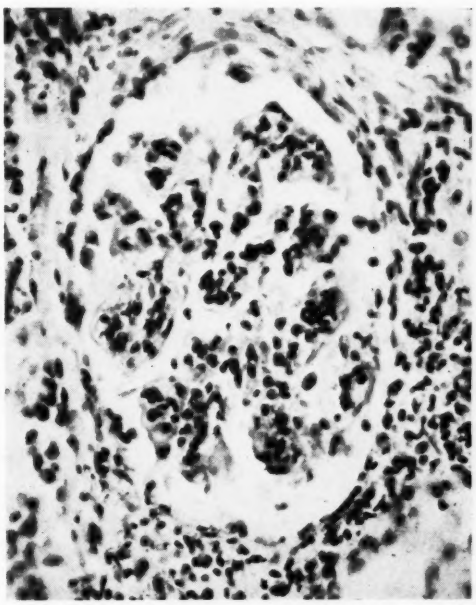

Fig. 2.—High power section of kidney from an instance of lupus erythematosus disseminatus. Note characteristic "wire loop" arrangement in the glomerulus and fibrinoid degeneration of connective tissue at lower end of section.

petechiae on the skin, renal manifestations, and evidence of sterile endocarditis. The lesions may involve the mural or valvular endocardium. Collagen degeneration of connective tissue occurs in these areas. These masses of connective tissue extend the endocardium outward, producing sterile nodular verrucae which differ from those seen in rheumatic fever. Blood cultures are negative. There are no Aschoff bodies in the myocardium.

There is another instance of collagen involvement of the mural or valvular endocardium. Its pathology is identical with that described under lupus erythematosus.

SCLERODERMA

Scleroderma is a disease, manifest by diffuse induration and immobility of the skin with pigmentation, sclerodactylia, and symptoms of arthritis. The pathologic lesion is a dense sclerosis of the connective tissue with the resulting clinical syndrome of weakness, weight loss, and gradually increasing mechanical interference with function. Occasionally there is development of pleurisy, pericarditis, dysphagia, and renal manifestation. Pathologic changes in the viscera are similar to lupus erythematosus. However, sections of the skin and of the esophagus show massive and diffuse increase in the connective tissues. The elastic fibers are destroyed. The corium shows collagen hypertrophy with obliteration of the papillae. Particularly, the smaller arterioles show thickening of the intima and some hypertrophy of the smooth muscle. The glomerular blood vessels undergo fibrosis. There is fibrinoid degeneration in serous membranes. Since the smaller blood vessels are usually involved, it is thought that connective tissue increase may also be due to diminution of local blood supply.

Little is actually known about the etiology of this disease. Efforts have been made to relate it to the endocrine glands (adrenals and parathyroids) and the sympathetic nervous system. It is thought that infections and toxic factors may play a role in its pathogenesis. There is no proof of an allergic etiology.

CASE REPORT

A. J. B., a white male, aged 53, was admitted to the United States Veterans Hospital, Aspinwall, Pa., on Aug. 23, 1947. In 1936, he first noticed that on exposure to cold and dampness the fingers became pale and numb. These symptoms disappeared on warmth. Following the pale color and numbness, the skin became bluish, then red, and eventually returned to the normal color. About 1938, he first noticed his skin was becoming thick and he had difficulty in completely opening his mouth. About 1940, the skin of the chest appeared changed and was shiny and somewhat smooth. The skin on the hands, forearms, and chest became tight and leathery, and of a dark color. There were some mild changes on the legs. Limitation of motion in the upper extremities appeared. The distal phalanges of the fingers became necrotic and shortened. In 1943, the patient began to notice exertional dyspnea, orthopnea, and ankle edema, with pain in his hands and frequent infections of the skin. By 1944, the entire skin was involved in the process which progressed slightly since then. About two years previous to entry, he began to notice difficulty in swallowing accompanied with some vomiting.

Physical examination revealed the skin to be tight over the face and skull, loss of eyebrows, and inability to completely open his eyes and mouth. The extremities showed muscle atrophy. The skin over the entire body, but particularly over the extremities, face, and chest, was bronzed, hardened, dry, and atrophic. Several ulcers were noted

particularly over the olecranon processes and on the distal phalanges of the fingers. Sclerodactylia of both hands was present. The left fifth toe was becoming gangrenous. The right elbow was fixed.

Laboratory examinations revealed the presence of albumin and granular casts in the urine, marked secondary anemia, and electrocardiographic changes suggestive of myocardial involvement. Barium studies showed a stricture of the esophagus approximately one inch above the diaphragm. Roentgenogram of the hands showed proliferative changes, narrowing of the joint spaces, and osteoporosis.

The course in the hospital was downhill. The patient developed many trophic ulcers and died of esophageal perforation into the pleural cavity.

Necropsy performed on Oct. 31, 1947, revealed the following positive findings.

The skin showed moderate brawny discoloration throughout. It was shiny particularly over the face, upper part of body, and the bony prominences. The upper limbs were ankylosed. The forefinger of the left hand showed ulceration over one of the phalangeal joints. The nails were distorted. Ulceration was also present over the left ear, left elbow, and forearm.

Thorax.—The lungs were bound by numerous adhesions but were partially collapsed. The left pleural space contained 500 c.c. of dark greenish-black material, evidently gastric content. In the right pleural space was 200 c.c. of serosanguineous fluid. The left pleura was thickened and layered with pliable exudate and gastric contents. The left lung weighed 550 grams and was boggy and blue-black in color. The bronchi were sacculated. Just below the hilus was a rent in the lateral aspect of the mediastinum. The right lung weighed 825 grams. It appeared atelectatic and showed the same major pathologic changes noted in the left lung. The heart was small. There was some fibrinous material on the epicardium. The myocardium showed flecks of pale grayish material throughout the substance.

Abdomen.—The esophagus was ulcerated at the esophageal-gastric juncture. The ulcer was continuous with a hemorrhagic sinus tract which proceeded upward and to the left, opening through the mediastinal rent into the left costal space. This resulted from a chronic ulcer. The cortices of the kidneys were finely granular.

Microscopic examination revealed the following positive findings.

Brain.—Sections of the cortex showed focal areas of calcification and minimal collagen changes in the media and adventitia of the small arteries. In addition, there were focal areas of encephomalacia. There were occasional areas of capillary hemorrhage and neuronal degeneration. A single granulomatous nodule composed of epithelioid cells in the posterior column of the spinal cord was present.

Skin.—The epidermis was flat and atrophic. The rete pegs are short and blunt and the papillae were absent. The corium contained a dense hyaline acellular material (Fig. 3).

Trachea.—The trachea showed necrosis of the mucosa, and changes of a hyaline nature in the peritracheal tissue.

Lungs.—The pleura was covered in many sections by a broad zone of acute inflammatory exudate. The pulmonary parenchyma was fibrotic, frequently hyalinized, and without architectural definition. There were acute miliary abscesses, small zones of infarctions and areas of bronchiectasis.

Heart.—There was an acute pericarditis. The myocardium showed many small areas of fibrosis. The coronary arteries revealed hyaline change in their walls which continued in the surrounding tissue.

Esophagus.—Sheets of amorphous acellular hyaline material appeared between and displaced parts of the wall beneath the mucosa. There was some perivascular round-cell infiltration.

Liver.—There was a thickened capsule containing both fibrous and acellular hyaline zones. There was also hyaline deposition in the portal areas.

Kidneys.—There was increased cellularity of the glomeruli with some patchy hyaline thickening. Vascular changes were prominent throughout the kidney with some of the cortical arteries obliterated. The media and adventitia were predominantly involved with fibroblastic change.

The anatomical diagnoses were: scleroderma; ulceration of esophagus with perforation; acute mediastinitis; bilateral hydrothorax; pulmonary edema and congestion.

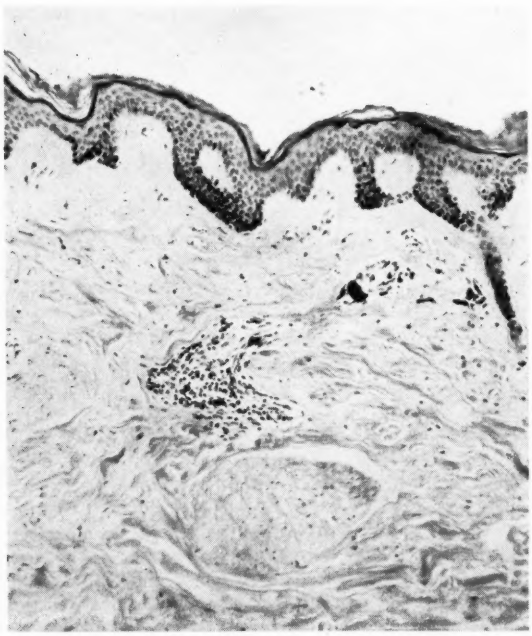

Fig. 3.—Section of skin from a case of scleroderma. Note increase in connective tissue and flattening of the papillae.

RHEUMATIC FEVER

The clinical features of acute rheumatic fever are too well known to need repetition. The lesions occur in the myocardial perivascular and in the subendothelial connective tissue, as well as in serous membranes. There are small, subcutaneous nodules and small, gray nodules in the heart, Aschoff bodies. The pathologic findings in the myocardium are as follows: there is early fibrinoid degeneration of collagen; large multinuclear cells, lymphocytes and plasma cells; the lesions show a central necrotic area (collagen), an increase in fibroblasts and replacement fibrosis. Varying stages of development may be present. Cellular reaction indicates the more acute process, while fibrosis reflects the end result. Unlike in lupus erythematosus, the lesions of rheumatic fever (Aschoff bodies) are not found outside the heart. Nor are the glomerular changes so characteristic of lupus seen in rheumatic fever. The condition must sometimes be differentiated from lupus erythematosus, since fever and arthritis may be the only clinical evidence of lupus at one stage of the disease.

Rheumatic fever is related to hemolytic streptococcal infection. However, the organism is rarely found in the acute lesions. The exudative lesions in the joints yield fluid which is sterile. Because of this and because animals infected with the streptococcus become very sensitive to the organism or its secretory products, Swift[2, 3, 4] suggested the possibility that rheumatic fever is a form of

bacterial sensitization enhanced by the presence of infection. There is considerable experimental proof offered by Rich in this connection. Rich and Gregory[6] showed that sensitization of rabbits with horse serum or egg albumin produces endocarditis and arthritis as well as multiple focal lesions in all layers of the myocardium. There is swelling and fragmentation of fibers with collagen degeneration bordered by multinuclear cells resembling the Aschoff bodies of rheumatic fever. Furthermore, the coronary arteries of these experimental animals show an endarteritis which is similar to rheumatic coronary arteritis. In some instances there may result considerable sclerosis of the coronary artery due to proliferation of the intima simulating arteriosclerosis.

The relation of rheumatic fever to hypersensitive phenomena is further emphasized by the following: the resemblance between rheumatic arteritis and the lesion of periarteritis nodosa, the latter condition being frequently a manifestation of allergy. Rheumatic fever also resembles serum disease in the following respects: both show fibrinoid degeneration of collagen, urticaria, erythema, purpura, eosinophilia, arthritis, and fever. The fluid in the joints of patients with rheumatic fever and serum disease is sterile and is cytologically similar. Improvement follows in both conditions from the administration of salicylates. The pathologic lesion of migratory pneumonitis seen in rheumatic fever is characterized by sterile, exudative, hemorrhagic changes with capillary thrombosis and alveolar necrosis. These same changes may be observed in experimental anaphylaxis, in serum sickness, and sulfonamide sensitiveness.

Rheumatoid arthritis, while related to the other conditions described in this paper, is separated clinically from rheumatic fever in that there are joint deformities. Rheumatic fever is an acute condition and as a rule is not accompanied or followed by a deforming arthritis. It produces definite valvular and myocardial lesions. None of these findings have been considered to characterize rheumatoid arthritis. And yet the question naturally comes up, whether it is not possible that the difference is more apparent than real; that the same antigen may produce a cardiac lesion in one case and an arthritic lesion in another—much the same as in allergic manifestations the same antigen may produce asthma in one patient and an atopic dermatitis in another. It should be pointed out that focal degeneration of collagen is found in both rheumatic fever and rheumatoid arthritis, also that patients with rheumatoid arthritis frequently present valvular lesions at post-mortem examination.

PERIARTERITIS NODOSA (PANARTERITIS, PERIARTERITIS)

Periarteritis nodosa was first described by Kussmaul and Maier in 1865[27] and later reported in detail by Boyd.[28] It is characterized by protean manifestations, including prolonged, severe weakness, fever, muscular pains (cramps), loss of weight, abdominal symptoms, polyneuritis, enlarged liver, signs of heart failure, microcytic anemia, and renal insufficiency. The onset is sudden. It affects males more often than females. Tender nodules may appear along the superficial arteries and, because of this and the associated eosinophilia, the condition may be confused with trichinosis. The clinical diagnosis is difficult. The condition is suspected if any of the above symptoms are found in association

with a long-continued illness, especially bronchial asthma and high eosinophilia. Biopsy makes the diagnosis definite. The disease is usually fatal, although occasional recoveries have been reported.[34, 37, 38]

The medium- and small-sized arteries are involved. There is no involvement of connective tissue elsewhere. The entire blood vessel wall may be affected. During the acute and subacute stages there is edema and fragmentation of fibers and cellular infiltration. There are at first polymorphonuclear leucocytes, and later lymphocytes, round cells, plasma cells, and eosinophiles. The internal elastic membrane is ruptured; intimal proliferation and degeneration occurs and this may lead to thrombosis with or without canalization. When thrombosis is complete, infarction of the related tissues occurs. The periarterial and adventitial layers of the blood vessel show evidence of fibrinoid degeneration of collagen, for there is laying down of fibrin and fragmentation of the elastic fibrils. Necrosis of the media may take place with hyaline degeneration so that small aneurysms are found. These either undergo fibrosis or rupture and bleed.

There is considerable experimental and some clinical evidence to indicate that periarteritis nodosa may be related to hypersensitiveness. This was suggested by Cohen and associates,[29] Wilson and Alexander,[30] Rackemann and Greene,[31] and Rosenak and Maschmeyer.[32] Masugi and Isibasi[21] produced lesions of periarteritis nodosa in animals sensitized to egg white. Rich[33] has demonstrated that the induction of serum disease in rats is accompanied by the production of periarteritis nodosa. He has further shown that intravenous injection of rabbits with sterile horse serum produces lesions of periarteritis nodosa. He also reported its presence in post-mortem examinations of five patients who had serum disease as a result of serum therapy for pneumonia.[7] In one of these instances sulfonamides were administered. Rich further cites the case of a patient on whom a skin biopsy was done and the diagnosis of squamous cell carcinoma of the scrotum was made. Following operation, sulfonamides were given to control infection and a drug reaction developed which proved fatal. Post-mortem sections from the same skin area, as well as from the viscera, showed evidence of fresh lesions of periarteritis nodosa. This would indicate that the lesions possibly developed as a result of drug sensitivity. Goodman[34] recently reported a case of periarteritis nodosa due to sulfadiazine sensitivity. Similar lesions may develop as a result of sensitization to iodine[35] (one post-mortem report in a patient who developed fever and eosinophilia following iodine therapy). Allergy to thiouracil, dilantin, and possibly aspirin may give rise to analogous changes. Reimann[36] suggested the possibility of periarteritis nodosa being brought about by sensitivity to trichina antigen by reporting two instances of the disease in patients with trichinosis. It would seem, therefore, that bacterial allergy, drug sensitivity, injection of foreign sera, and sensitization to parasites, may be etiologic factors in the development of periarteritis nodosa.

CASE REPORT

W. A. B., a white male, aged 48, was admitted to the medical service of the Presbyterian Hospital, Pittsburgh, Pa., on May 4, 1946, complaining of "pain in stomach" and "soreness of the leg." His legs began to get numb in April, 1946. Gradually, he lost

sensation in both legs. His appetite became poor with occasional nausea and vomiting. There was a history of paroxysmal attacks of severe asthma. His mother died of diabetes.

Physical examination revealed irregular elevation of temperature (99° F. to 101° F.). Blood pressure was 160/85 mm. There was localized tenderness in the epigastrium and in the right upper back.

The positive laboratory findings were as follows: urine showed a cloud of albumin; blood count: red blood cells, 3,500,000; hemoglobin, 62 per cent; white cells, 7,000; blood nonprotein nitrogen, 54 mg. per cent; sugar, 167 mg. per cent; creatinine, 2.45 mg. per cent; chlorides, 427 mg. per cent; serum amylase, 4 units; plasma proteins, 9.39 Gm. per cent. Sputum revealed predominance of streptococci and gram-negative bacilli but no tubercle bacilli. Several days before he died (May 28) the red cell count was 2,400,000; white cells, 23,000 with 90 per cent polymorphonuclear leucocytes; and nonprotein nitrogen, 100 mg. per cent.

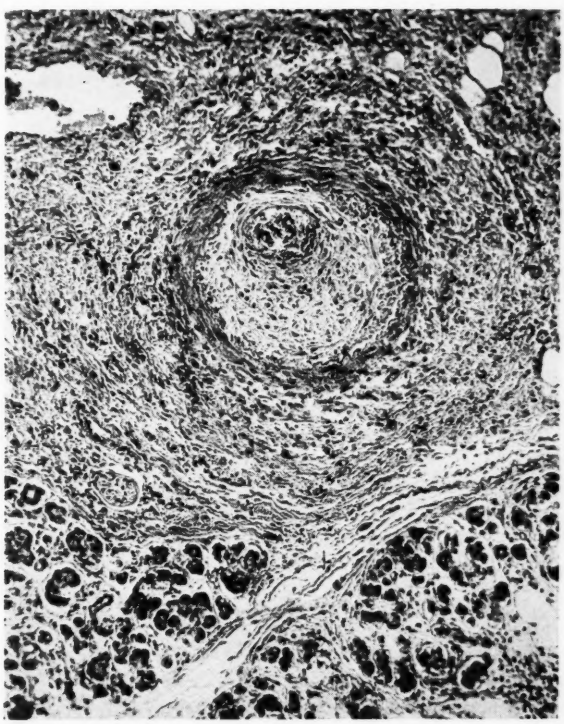

Fig. 4.—Periarteritis nodosa. Section of pancreas showing medium-sized blood vessel with marked proliferation of intima and collagen degeneration. The lumen is extremely narrowed. There is partial thrombosis with canalization. The elastic lamina is indistinct and mostly replaced by fibrous connective tissue. The media shows fibroblastic changes with hyalinization. The adventitia shows proliferation and leucocytic infiltration.

The following is a summary of his course in the hospital: the patient continued to be febrile and complained of pain in the epigastrium and in the calves of both legs, which was diagnosed as thrombophlebitis. On May 13, ligation of femoral veins was done. He began to complain of severe pain in right upper quadrant and on May 27, he was operated upon. There was found an enlarged liver, chronic pancreatitis, distended gall bladder, and massive retroperitoneal hematoma. The same day he developed a severe asthmatic attack which responded to epinephrine. On May 30, severe left upper quadrant pain with marked abdominal tenderness appeared. He became weaker, the pulse rose to 144. The patient became comatose and died soon thereafter.

Necropsy revealed the following positive findings.

Abdomen.—There was a large hematoma on the right side behind the liver and another on the left side in the kidney zone. The liver was large. There was considerable passive congestion and there were several blood-containing cysts under the cortex. In addition, there was a pale parenchymal zone about 1 cm. in diameter under the capsule. The spleen was large, firm, and bright red. Numerous nodules were noted in the head and tail of the pancreas, which was adherent to the hematoma noted above. In one section were areas of fat necrosis. The kidneys were large, soft, and nodular, and in close association with the hematoma. The capsule of the kidney was apparently the capsule of the hematoma. The cortices were thin. There were numerous hemorrhages in the medullary portion.

Microscopic examination revealed the following lesions:

The coronary artery showed intimal proliferation. There was scattered perivascular fibrosis.

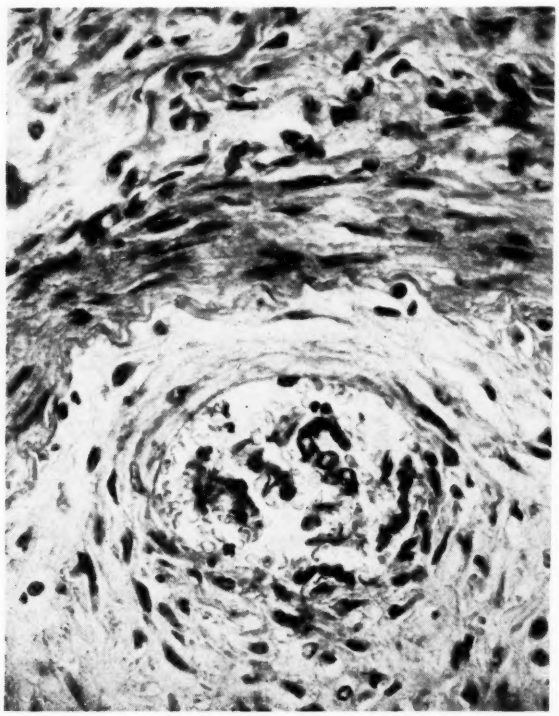

Fig. 5.—Periarteritis nodosa. High-power section of blood vessel showing desquamated endothelial cells and debris lying loose in the lumen. There is endothelial cell and fibroblastic proliferation of the media with hyalinization. Note collagen degeneration.

Abdomen.—Throughout the liver were foci of acute and chronic inflammatory cells with hemorrhage and fibrosis surrounding the central vein. Fibrosis was marked throughout the organ. One section revealed a large hematoma surrounded by fibrous tissue and acute, chronic, and inflammatory cells. The blood vessels showed thickening with intimal proliferation and marked perivascular infiltration of inflammatory cells. Areas of infarct were noted in one section. There was considerable interstitial hemorrhage in the spleen. Areas of diffuse infiltration of fibrous connective tissue appeared in the pancreas. Several large areas of necrotic tissue were noted surrounded by acute and chronic inflammatory cells and in association with fat necrosis. The arteries showed intimal proliferation, nodular scarring of the adventitia, and perivascular infiltration by inflammatory cells. (Figs. 4 and 5). A section of kidney revealed scattered but heavy infiltration of chronic inflammatory cells. Several areas of hemorrhage were noted surrounded by concentric rings of hyaline, fibrous tissue, and

chronic inflammatory cells. The arteries show the same pattern as noted in the previous descriptions. The arteries of the adrenals revealed the same pathology as were noted in the liver and kidney. Lymph nodes showed proliferation of the reticulo-endothelial cells.

The major anatomic diagnoses were: periarteritis nodosa of pancreatic, hepatic, renal, adrenal, and prostatic arteries, and aorta; massive bilateral perirenal hematoma (subcapsular); multiple hemorrhages of kidneys (parenchymatous); acute pancreatitis with fat necrosis; hemorrhagic central necroses of liver; infarct of liver; and hematoma of liver.

Notanda.—Death resulted from unusual complications of periarteritis nodosa, manifested by widespread arterial lesions of the abdominal viscera. The hepatic, pancreatic, and renal complications were the direct cause of death, the most significant being the massive bilateral renal hemorrhages.

DERMATOMYOSITIS

This is a comparatively rare, chronic, and usually fatal disease which involves the skeletal muscles first, and later the subcutaneous tissues and skin. The onset is insidious. The etiology is unknown. The condition occurs in middle life. It is characterized by weakness, tenderness of the muscles, swelling, edema, painful motion, and eventual atrophy. There may be fever, leucocytosis, occasional eosinophilia, and albuminuria. The spleen is enlarged. The face may become erythematous and simulate lupus erythematosus. The characteristic findings consist of edema, dermatitis, and myesthenia. Later in the disease, contractures occur about the elbows and knees, due to atrophy and fibrosis.

Pathologically there is cellular infiltration of muscle. The arteries and arterioles are thickened by a massive increase in connective tissue in the arterial wall. The lumen is reduced in size and this in turn may decrease the blood supply to the skeletal muscles leading to the manifestations described above. The morphologic pathology is identical at least in the earlier stages with scleroderma with which this condition is frequently confused. Trichinosis is ruled out by biopsy. Treatment is unsatisfactory. Some patients show sunlight sensitivity. Other than this there is no evidence that allergy plays a role in the causation of this disease.

NEPHROSCLEROSIS

Kidney lesions characteristic of collagen disease are of course frequently found in lupus erythematosus and periarteritis nodosa; experimentally these lesions may be produced in rabbits by injecting them with kidney extract and streptococcal toxin, or by the Goldblatt experiment. Collagen degeneration is also to be observed in other renal conditions, i.e., the kidney of the Kimmelstiel-Wilson syndrome and in malignant nephrosclerosis, neither of which conditions have an allergic etiology. In Kimmelstiel-Wilson syndrome, the kidney lesions bear certain resemblance to collagen disease, although there is a difference in the distribution and size of the lesion. Radiation and experimental wrapping of the kidney in cellophane may produce necrotizing changes in the arterioles, lesions similar to periarteritis nodosa.

SCLEREMA NEONATORUM (SCLERODERMA)

This condition may also be grouped under the heading of collagen disease. It is relatively rare. It occurs in infants and children who show a brawny in-

duration and progressive edema of the subcutaneous tissue over the shoulders and anterior surface of the lower legs. The condition is fatal. Pathologically, there is some thickening in the subcutaneous layers accompanied by collagen increase and large individual fatty alveoli. The etiology is unknown.

THROMBOANGIITIS OBLITERANS

The clinical manifestations of this condition need not be outlined in this paper. It usually involves one of the larger arteries of the extremities. There is a marked inflammatory reaction characterized at first by leucocytic infiltration and later by the presence of giant cells. The vessel wall is thickened and may show fibrinoid degeneration of collagen and fibrosis. The lumen becomes smaller or even occluded. The etiologic relation of this disease to allergy is emphasized by Harkavy[39] who was able to show positive skin reactions specific for tobacco in a large series of such patients. This evidence is suggestive although not conclusive.

COMMENT

A review of the conditions discussed above reveals certain pertinent facts and offers an opportunity for speculation in connection with our present knowledge of diffuse collagen disease. This group of diseases is obviously associated with common pathologic changes in the connective tissue system. Since this system is widely distributed in all organs of the body, it follows that the clinical manifestations of collagen disease will be different and widespread. Hence, clinical entities, each separate and distinct, are included under this heading.

Allergy to tobacco may be important in connection with thromboangiitis obliterans. In most instances however there is no clearly known etiology.

Hypersensitiveness (allergy) and collagen disease are often somewhat related. Fibrinoid degeneration of collagen is seen in the Arthus phenomenon as well as in bacterial anaphylaxis. Serum sickness, which certainly is a manifestation of allergy, is characterized at times by collagen disturbance. There is a report of a case of lupus erythematosus following the injection of foreign serum in man. Furthermore, this condition is thought to be related to a possible *id* reaction[24] and sensitivity to light. Periarteritis nodosa has been demonstrated in man both after the injection of foreign sera and the administration of sulfonamides. Its allergic basis is further indicated because of its association with asthma, urticaria, and eosinophilia. The possible allergic basis of rheumatic fever is suggested by some of its allergic manifestations, namely, urticaria, eosinophilia, and erythema multiforme. Furthermore the clinical manifestations of rheumatic fever, endocarditis, and arthritis and its pathologic lesions may be reproduced experimentally by sensitization.

In spite of the above stated evidence, namely, that allergy may occasionally play an etiologic role in collagen disease, it should not be assumed that the presence of collagen changes in man are necessarily and always caused by hypersensitivity. Common pathology does not necessarily bespeak a common etiology (Klemperer). One might as well assume that all conditions associated with eosinophilia are allergic simply because many allergic conditions are character-

ized by eosinophilia. Baehr and Pollack[16] point out that mild collagen degeneration may be caused by factors other than allergy, i.e., infections, experimental hypertension, and exposure of tissue to noxious agents such as heat and chemicals.

SUMMARY

1. Collagen disease includes a variety of separate and distinct clinical conditions of varied and multiple etiology with a common pathologic picture, namely, fibrinoid degeneration of collagen.

2. There is some evidence, both clinical and experimental, which indicates that the development of some of these conditions may be closely related to the phenomena of hypersensitiveness.

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DETERMINATION OF THE SPECIFICITY OF HISTOPLASMIN AND COCCIDIOIDIN AS TESTED ON 356 ALEUTS OF THE PRIBILOF ISLANDS

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IN THE summer of 1946, the opportunity arose to examine a group of natives on the Pribilof Islands in the Bering Sea, 200 miles off the mainland of Alaska. This was done at the request of the United States Government, specifically the Department of Interior under whose jurisdiction these people live as wards.

The original study and investigation were carried out to determine the cause of the loss of teeth in these natives. However, the opportunity arose to also test a relatively isolated and protected group of people with specific allergenic materials, the specificity of which was somewhat in question.

A brief description of the natives and the climate may suffice to give a picture of the problems encountered in this study. The Pribilof Islands are made up principally of two islands, St. George and St. Paul, lying 240 miles north of Dutch Harbor in the Bering Sea. These islands are separated by 40 miles of water and intercommunication by radio or boat is the only means of contact. The natives inhabiting these islands are called Aleuts and are regarded as a branch of the Eskimo who migrated across the northern wastes of Alaska to the Aleutian Islands and thence up into the Pribilof group. For those interested in the origin and migration of these peoples, one may refer to the symposium on dental caries.[1-7] There are present some diseases classified as allergic in character, as we understand them, consisting mainly of eczema, asthma, and hay fever. Plant life abounds on both islands although it is somewhat different in character from that which we find on the Alaskan mainland, and definitely different from that of the States.[8]

SKIN TESTS

Skin testing was done in two parts:

1. A survey for tuberculosis was carried out by tuberculin tests made on all the natives present on St. George and St. Paul Islands. It is well known that the death rate for tuberculosis in Alaska is probably the highest in the world, namely 359.1 per 100,000 for 1945-1946. The rate for the United States during this period was 40.1.[9] Three hundred fifty-six natives were skin tested with tuberculin. The reactions were rather severe. The majority of the natives showed rather marked induration, redness, and discomfort. Because of the severity of the reaction, the tuberculin was diluted further to one-half the strength of that originally used in the first dose. See Table II. This fact should be emphasized since, as will be pointed out, the natives did not react to histoplasmin or coccidioidin. One would expect the natives to react as strongly to these extracts as well as to the tuberculin should they have come in contact

with the specific disease. Although this paper does not deal with the problem of tuberculosis, all those with positive skin reactions were fluoroscoped, and all suspects were x-rayed. Two active cases of tuberculosis were thus discovered.

2. The other two materials used consisted of histoplasmin and coccidioidin.* It is interesting to note that these natives had never left the islands except in 1943 when they were moved to an Army community at Funter Bay. This settlement is just south of Juneau, Alaska. The natives were completely segregated and had no access to roam further into the mainland. At this particular period, as far as could be determined, they had no opportunity to come into contact with sources of the infection for which they were to be tested. Two extracts were used to determine their specificity. At the time the natives were skin tested with tuberculin, they were also given 1:1000 dilutions of histoplasmin and of coccidioidin. A small group of the white population was used as controls. The white people had for the most part inhabited the southwestern or Pacific Coast states, or areas in which coccidioidomycosis prevails. All of the 356 natives skin tested, except one, gave completely negative results for both histoplasmin and coccidioidin. The one native whose test was positive, a 31-year-old woman, showed a reaction of 3 plus to histoplasmin. She gave no history of contact with dogs or other animals. Incidentally, no dogs are permitted on the islands because of their endangering the seal herd. There have been, however, several cats present on both islands.

TABLE I

SOLUTION	NO. OF NATIVES	NO. OF NATIVES REACTING	NO. OF WHITES	NO. OF WHITES REACTING
Tuberculin	356	94	18	14
Coccidioidin	356	0	18	3
Histoplasmin	356	1	18	0

TABLE II. NUMBER OF GRADED REACTIONS TO TUBERCULIN

GROUP TESTED	NUMBER	4 PLUS	3 PLUS	2 PLUS
White inhabitants	18	4	2	7
Native inhabitants	356	15	46	35

Of the eighteen white persons tested, three gave positive reactions to coccidioidin. All three had at one time been in the state of Kansas, two of them had lived in California, and the third in Washington. None gave a history of having had the disease or of reactions indicative of a subacute or subclinical type of infection. All of the natives giving negative reactions to histoplasmin and coccidioidin in strengths of 1:1000 were tested with solutions of 1:100 strength. No positive reactions were noted. See Table I.

From this work it appears that natives living in a noninfected area showed no positive skin reactions (with one exception), while one-fifth of the white population, although small, gave positive reactions to coccidioidin. These tests may indicate the need for further study to determine the specificity of this type of skin test. It does not as yet, in our opinion, answer the question of the

*Both materials were supplied by the National Institute of Health, Bethesda, Md., through the courtesy of Dr. Emmons.

specificity of histoplasmin since no known cases of either disease were tested or treated. This work does show that in a large series of tests made on people known not to have had the disease, the solution of histoplasmin gave consistently negative reactions. However, we do recognize the fact that active or known patients with the disease also must be tested to establish definitely the specificity of these extracts as has been demonstrated with tuberculin.

SUMMARY

1. Three hundred fifty-six natives and eighteen white personnel were tested with tuberculin, coccidioidin, and histoplasmin.

2. Severe reactions were noted after injection of the tuberculin solution.

3. No native showed a reaction to coccidioidin.

4. Only one native reacted to histoplasmin.

5. Of the eighteen white personnel, three reacted to coccidioidin, and none, to histoplasmin.

6. This large series of tests indicates the consistency of negative reactions in persons not having come in contact with the disease.

7. We recognize the fact that histoplasmin must be tested further on patients known to have had or to have come in contact with the disease to establish the specificity in question.

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EOSINOPHILIC PLEURAL EFFUSION AND PERICARDITIS WITH EFFUSION IN AN ALLERGIC SUBJECT*

(Report of a Case Treated With Pyribenzamine)

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DISEASES of the heart, lungs, and blood vessels should not be invariably regarded as having been caused by degenerative processes, infections, or toxic agents. A hyperergic or allergic mechanism may produce an identical clinical picture.[7]

Reports of febrile disease involving the heart, lungs, and pleura due to allergic response by vascular structures are still rare. We were able to find only one case[1] in which the known allergic manifestations (rhinitis and asthma) disappeared with onset of the febrile disease and returned following recovery, indicating an alternation of shock organs. No cases were reported in which treatment with antihistamine drugs was attempted, although their use has been suggested.[2]

The following case exemplifies the occurrence of arrhythmia, pneumonitis, pericarditis, and pleuritis with effusions in a subject whose asthma disappeared at onset, was absent during the sixty days of the illness, and reappeared after recovery. Recovery was coincidental with the administration of large doses of Pyribenzamine.

CASE REPORT

C. G., a 49-year-old unmarried white woman, entered the hospital on Jan. 7, 1948, with pain in the left shoulder, neck, and chest, accentuated by deep breathing, cough, and fever of 102° Fahrenheit. The onset of this illness was five weeks prior to admission, when she developed mild anterior chest pain and rapid pulse. An electrocardiogram revealed, within the time occupied by taking the first three leads, bigeminy due to nodal premature contractions, coarse auricular flutter, and auricular fibrillation (Fig. 3, 12/1/47). Quinidine was administered by her physician and within twenty-four hours the arrhythmias and chest distress disappeared. Two weeks later (three weeks prior to admission) there was a recurrence of the above symptoms associated with mild sore throat. The patient then had no complaints until the day of admission.

Past history revealed that she had had repeated attacks of bronchitis in childhood during the winter months in New York City. The attacks were characterized by cough, dyspnea, and fever but diminished in severity as she grew older. In 1940, she moved to Florida and felt well for approximately two years. Asthma first appeared in 1942, persisted throughout the winter months, and disappeared in the summer when she returned North. Allergic studies were refused by the patient and symptomatic treatment kept the asthma under moderate control. Potassium iodide was used constantly from 1943 to the onset of this illness.

In 1928, a thyroidectomy for exophthalmic goiter was performed. Poor results necessitated the operation to be repeated six months later, and due to the recurrence of toxic symptoms the operation was again performed in 1945. The patient has had no evidence of hyperthyroidism since the last operation and repeated basal metabolic rate determinations have been within normal limits. She did not use tobacco or alcohol.

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The family history included "sneezing spells" in the paternal grandmother, and hay fever in one brother and in the brother's child.

At the time of admission the patient did not appear acutely ill. The temperature was 102° F., pulse rate, 100 per minute and regular in rhythm, the respiratory rate was 26, and blood pressure was 110/60. There was marked bilateral exophthalmos. The nasal septum was deviated to the right, mucopurulent discharge was noted on the left, and there was no transmission of light through the left maxillary sinus. The pharynx was mildly injected. The chest wall was considerably enlarged in the anteroposterior diameter and expiration was slightly prolonged. The heart sounds were good, there were no murmurs, and rhythm was regular. There was no abnormal dullness to percussion of the chest. On auscultation crepitant râles were heard at the left posterior base. The abdomen and extremities were negative. There were no palpable nodules, enlarged lymph nodes, or edema.

On admission the red blood cell count was 4,100,000 per cubic millimeter and the hemoglobin level was 77 per cent Sahli. The leucocyte count was 11,000 with 79 per cent polymorphonuclear leucocytes, 20 per cent lymphocytes, and 1 per cent eosinophiles. The corrected sedimentation rate (Westergren) was 40 millimeters. A roentgenogram of the chest revealed a small striated pneumonic infiltration in the left lower lobe (Fig. 1, 1/7/48).

On the second day of hospitalization there was a recurrence of a rapid irregular heart rhythm for which quinidine was administered. The arrhythmia ceased before an electrocardiogram could be obtained. Penicillin by aerosol and intermittent intramuscular injections were begun on the day of admission and continued in doses of 300,000 to 800,000 units for thirty hospital days. Streptomycin, from 1 to 1.5 Gm. daily, was used in addition from January 22 to February 10. Antibiotics were omitted from January 29 to February 2 (Fig. 2).

There was no evidence from the character of the fever chart, or from the clinical course, that these antibiotics were therapeutically effective. The patient proved sensitive to sulfadiazine and this was discontinued after one dose on January 29. A history was then obtained that exfoliation of the skin and itching had also occurred several years previously when the drug was given.

With the exception of low-grade fever the patient was symptom-free until January 16, the ninth hospital day, when a mild rise of temperature occurred and on examination a precordial friction rub was heard. A roentgenogram of the chest revealed a considerable increase in the size of the cardiac shadow (Fig. 1, 1/15/48). The total white blood cell count was 7,500; polymorphonuclear leucocytes, 59 per cent with no juvenile forms; and lymphocytes were 41 per cent. The patient's general condition was good. She was alert, interested, and completely without subjective complaints. During the next several days the fever slowly subsided.

On January 22, the fourteenth hospital day, pain in the shoulders, moderate productive cough, and an increase in temperature occurred again. On examination, the heart sounds were good and the rhythm was regular. There were dullness and diminution of breath sounds at the left base. A chest roentgenogram at this time revealed a small pleural effusion at the left base and no change in the enlarged heart shadow previously noted (Fig. 1, 1/23/48). Diagnostic pericardial and pleural taps were done but in each case only a few c.c. of what appeared to be blood were obtained. Smears and cultures of both fluids were negative for organisms on penicillinase media and examination of the centrifuged specimens for tumor cells by the Papanicolaou technique was negative.

Additional laboratory studies were made at this time. Examination of the sputum was not revealing. Repeated search of concentrated specimens for acid-fast bacilli was negative. Agglutinations for obscure fevers were negative. Guinea pig inoculation of the fluids obtained by chest taps were later reported as negative. The leucocyte count was 16,800 with 82 per cent mature polymorphonuclear leucocytes and 18 per cent lymphocytes. Bleeding and clotting time and platelet count were within normal limits. Prothrombin time was 84.6 per cent of normal.

During the next six days there was a day-by-day fall in temperature and improvement in the clinical symptoms. On January 30, the twenty-third day of hospitalization, however,

Fig. 1.—Roentgenogram on 1/7/48 shows a minute patch of pneumonitis at left base. On 1/15/48, effusive pericarditis; plus early pleuritis on 1/23/48; massive pleuritis with effusion on 2/12/48; subsidence of both processes on 3/5/48; residual pleural thickening, left base, on 5/24/48.

Fig. 1.—Roentgenogram on 1/7/48 shows a minute patch of pneumonitis at left base. On 1/15/48, effusive pericarditis; plus early pleuritis on 1/25/48; massive pleuritis with effusion on 2/12/48; subsidence of both processes on 3/5/48; residual pleural thickening, left base, on 5/24/48.

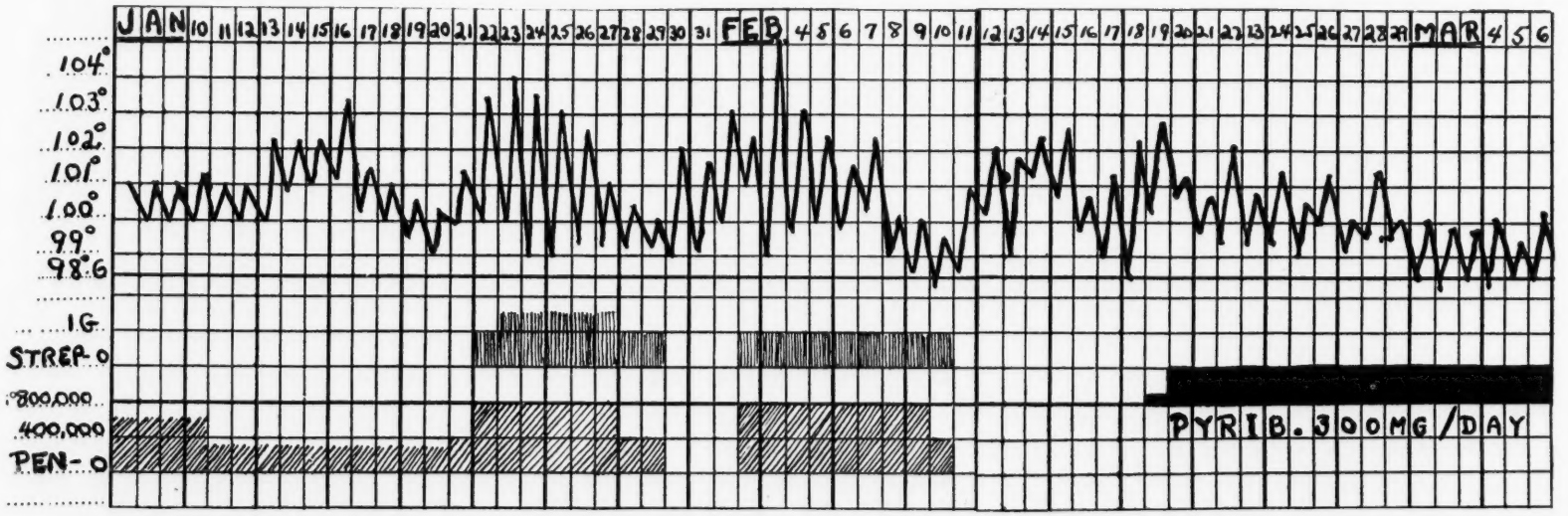

Fig. 2.—Temperature chart. Daily low and high temperatures are shown for the period of hospitalization. From January 7 to 13 oral temperatures are recorded, thereafter rectals.

The dosage of penicillin, streptomycin, and Pyribenzamine are indicated.

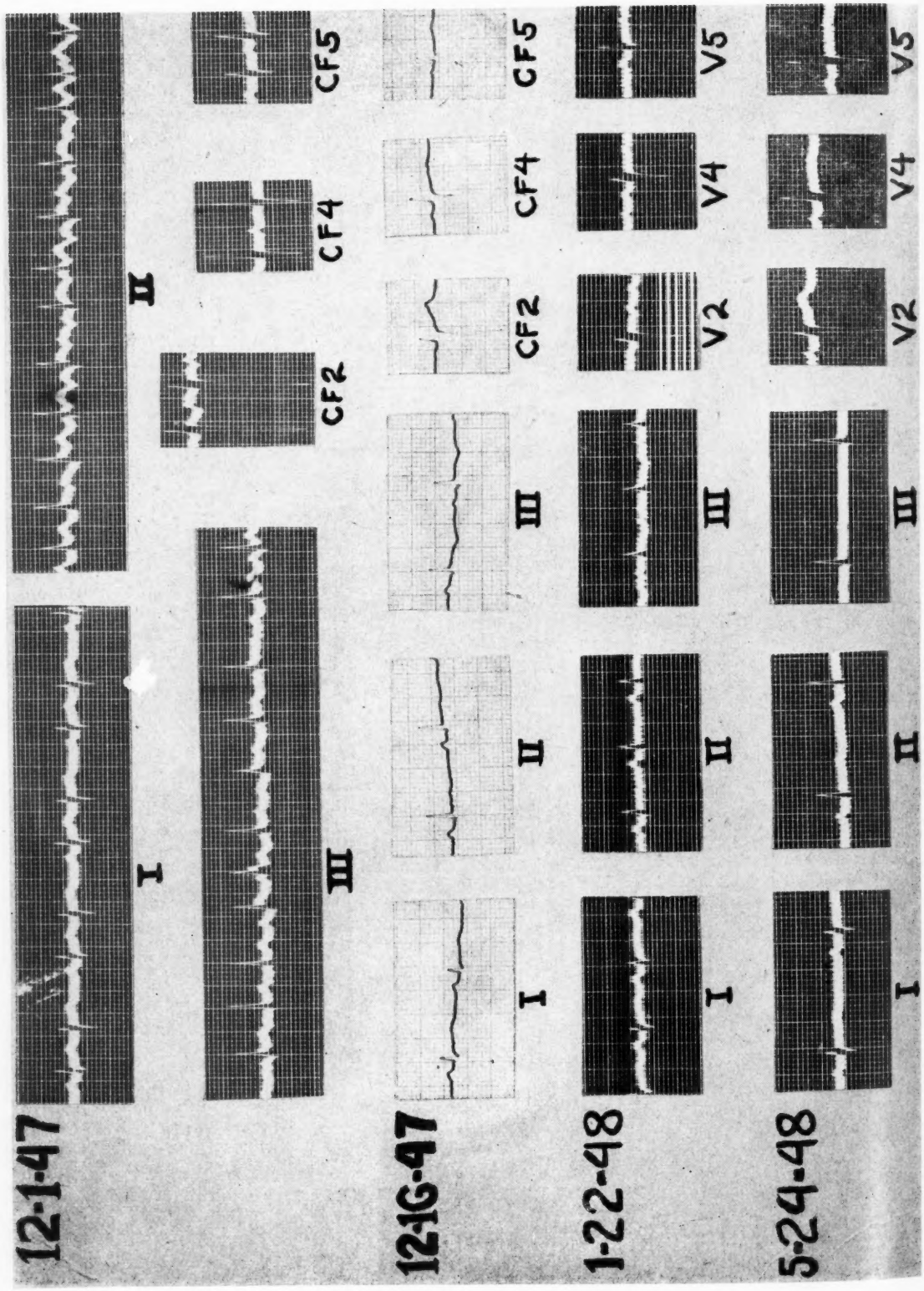

FIG. 3.—*(For legend see opposite page.)*

the presenting symptoms recurred again with a rise in fever. Over the course of the next nine days the temperature again dropped toward the base line.

On February 16, the fortieth hospital day, there was a sharp rise in temperature associated with the findings of dullness and diminished breath sounds in the lower half of the left chest posteriorly. A pleural tap was again performed and 1,200 c.c. of straw colored spontaneously coagulating fluid were removed. This accumulation of fluid was entirely asymptomatic except for fever. Smears, anerobic and aerobic cultures revealed the fluid to be sterile. The differential cell count of the fluid revealed 80 per cent eosinophilic leucocytes and 20 per cent lymphocytes. Special study of the cellular content showed the presence of numerous serosal cells observed in the process of phagocytizing the white blood cells and some flat filled mononuclear macrophages. No tumor cells were seen. Guinea pig inoculation, cultures, and direct examination were negative for tubercle bacilli, as were cultures for other organisms. Direct skin testing with pleural fluid disclosed no antigen. During the next two weeks, daily blood counts were within normal limits except that a variable number of eosinophilic leucocytes were observed, the greatest number amounting to 7 per cent.

On February 20, the forty-fourth hospital day, all medications were discontinued except Pyribenzamine, 200 mg. given in four doses. On the next day and each day thereafter for the remaining two weeks of the hospital stay 300 mg. in four doses were given daily. During this period there was a gradual decline of symptoms and fever, and on March 6, the fifty-ninth day, the patient was discharged from the hospital.

Within twenty-four hours of discharge there was a return of allergic rhinitis and asthma. It is important to note that before this illness, environmental change on three separate occasions had failed to relieve the patient. By history, trial and error, elimination diets, and skin tests by the dermal and intradermal techniques it was determined that sensitivity existed to beef, milk, tomato, house dust, and the carbohydrate fractions of several bacteria. A regime of allergic hygiene, elimination of offending foods, hyposensitization to house dust and a vaccine during the next few months were successful in preventing recurrence of asthma, but mild rhinitis persisted. It is interesting also to note that Pyribenzamine did not control the allergic rhinitis which developed after the patient's discharge from the hospital. The relation of these sensitivities to the acute illness herein described is unknown and can be determined only by the incidence of recurrence. Radical surgery for the maxillary sinusitis had been temporarily deferred pending her response to allergic therapy.

On May 24, 1948, the patient was re-examined by one of us (J. A. Oshlag). There were no symptoms or abnormal signs relevant to the cardiovascular or respiratory systems. A roentgenogram of the chest (Fig. 1, 5/24/48) revealed that the heart size had returned to that preceding the pericarditis, but the electrocardiogram (Fig. 3, 5/24/48) showed residual signs of the previous difficulty. Biopsy of the gastrocnemious muscle, at this time, revealed no abnormality.

COMMENT

The frequency of occurrence of allergic disease of the cardiovascular and respiratory systems has not been determined. Undoubtedly many cases properly belonging in this category have been classified as "etiology unknown." Others may have been incorrectly diagnosed, by an exclusion process, because the manifestations of this disease resemble better known infectious and degenerative disturbances.

Fig. 3.—(*For legend see opposite page.*)

Fig. 3.—Electrocardiogram on 12/1/47 demonstrates bigeminy due to alternating nodal premature contractions in Lead I, and impure flutter in Lead II, and short runs of fibrillation in Lead III.

On 12/16/47, abnormality is indicated by diminution of T_1, T_2 and CF_4.

The electrocardiogram of 1/22/48 shows low voltage, suggests coving of ST_1 and flattened T waves, compatible with pericarditis.

Residual signs are noted on 5/24/48, recorded more than two months after clinical recovery.

Reports of human cases, while rare at the moment, are appearing in the literature with increasing frequency, many being substantiated by autopsy material.[2-5] Klemperer has described some of these cases as a forme fruste of periarteritis nodosa.[6] In our case, additional speculation concerning the etiological factor is suggested by a case of periarteritis nodosa reported by Rich.[4] In his patient hypersensitivity to iodine was believed to have been the cause.

There is, furthermore, adequate animal experimentation to indicate that allergic disease of the cardiovascular system does occur. Klinge, Roessle, Jaeger, Rich, Gregory and others have produced fibrinoid degeneration in the component parts of the vascular system in animals by the injection of bacterial and nonbacterial antigens.[7] This lesion is typical of the hyperergic phenomenon.[8] It is noteworthy that this degenerative change is also characteristic of the diffuse collagen diseases.[9-11]

The responsible mechanism appears to be the establishment of the vascular apparatus as a major shock organ.[12] The course of the disease is dependent upon the reversibility or irreversibility of the pathological lesion.[13] Many cases follow a spontaneous course of recovery after repeated effusions.[14] The prognosis in such a case as the one presented is necessarily guarded.

SUMMARY

1. A case of pleurisy and pericarditis in a hypersensitive individual is described in which the significant features were the onset with cardiac arrhythmia, pneumonitis followed by pleurisy with effusion, and pericarditis with effusion, 80 per cent eosinophiles in the cell count of the pleural fluid, failure of reaction to the antibiotics, absence of proof of viral etiology, and recovery associated with the administration of Pyribenzamine.

2. It is not known whether the recovery was spontaneous or resulted from the use of this antihistamine drug. To our knowledge this is the first report in which an attempt was made, with apparent success, to utilize the antihistamine drugs in therapy in such a case.

3. These features, with the other clinical data discussed, even without positive pathological findings or the reproduction of the clinical picture by a specific agent, seem sufficient to add this case to the accumulating literature illustrating a hyperergic etiology of cardiovascular disease.

4. In the absence of death with postmortem studies or in cases of localized arteritis involving organs not readily accessible for biopsy, histological proof is impossible and reliance must be placed on clinical evaluation.

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NAIL DYSTROPHY DUE TO PLASTIC UNDERCOAT FOR HOLDING NAIL LACQUERS

ANDREW GEORGE FRANKS, M.D., NEW YORK, N. Y.

CASES of allergic eczematous reactions due to several preparations used as undercoats to nail polish or lacquer are appearing in dermatologic practice. In view of the paucity of published reports the following case is recorded.

J. M., a female, aged 34, was first seen May 27, 1948. At that time she complained of discomfort and deformity of the nails of both hands. This condition was present for a period of two weeks. She stated that several days previously she had had an undercoat, "Everon," applied to her nails. Examination showed that all the nails of both hands were involved (Figs. 1 and 2). The characteristic changes were the subungual hyperkeratosis and the varying discoloration of the nails, which were a red-blue to brown shade, chiefly on the distal ends. Some elevation of the free edges were observed. Skin changes were slight. She complained at the onset of tenderness and pain in the finger tips. Later her complaint was inability to use her finger tips properly.

Patch tests were done with Everon and its constituents; namely, a solvent, rubber, and resins. Positive reactions to Everon and the two of the four resins used appeared.

Fig. 1.—Everon discoloration of the nails.

COMMENT

A case of nail dystrophy caused by Everon is reported. Fanberg and Sharlit reported two cases with characteristic changes. Ten cases were seen by Sulzberger and his associates. They reported the clinical, histologic, and immunologic findings in detail. They believed that the solution of phenol-formaldehyde resins and synthetic rubbers in methyl-ethyl ketone caused a contact-type dermatitis of the nail bed and that this could account for the ungual dystrophy.

Fig. 2.—Dystrophy of the nails caused by Everon.

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Erratum

In the article, "Milker's Eczema," by Stephan Epstein (September, 1948), the prescription on page 340 should read as follows.

Vioform	0.6
Naftalan or dernaftan	1.5
Castor oil	3.0
Lassar's paste	
Boric Acid ointment—equal parts to make 30.0	
S: Apply and bandage	

American Academy of Allergy

REPORT OF THE FIFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF ALLERGY

HISTORIAN'S REPORT

The executive committee had three busy days preceding the regular meeting of the Academy in Atlantic City—hearing and considering various committee reports, and deciding on matters of policy and action. Space here permits mention only of matters of particular interest.

Dr. Alexander acquainted the executive committee with some of his problems. His previous request for two associate editors was approved. Drs. William Sherman and Francis Lowell were the choice of the committee for these posts. Dr. Bram Rose and Dr. Samual Bukantz were selected to replace outgoing members of the editorial board, Dr. M. B. Cohen and Dr. Louis Tuft. It was decided to terminate the present contract with The C. V. Mosby Co. for publication of THE JOURNAL OF ALLERGY, but to leave the matter open for renegotiation of contract terms.

Dr. Hooker outlined an extensive research problem on house dust antigen to be carried out under supervision of Dr. Dan Campbell. Dr. Simon's committee on inhalant allergens should be given cooperation by each member of the Academy.

The scientific session was better attended than usual. Outstanding contributions were the memorial lectures, "The Immunology of Virus Disease," by Dr. Thomas Francis, Jr. in memory of Dr. Harry D. Donnally, and "An Experimental Approach to Psychosomatic Phenomena in Rhinitis and Asthma," by Drs. Holmes, Goodell, Wolf, and Wolff, dedicated to Dr. Robert Lamson.

The business meeting proceeded with an unusual spirit of harmony. This is doubtless the result of recent efforts to democratize the organization of the Academy. Members have been kept informed of the progress of the committee on an independent board of allergy. Chairman Piness reported that this committee had had a fair hearing and that he believed progress was being made.

The place and date of the next meeting were not definitely decided, although Los Angeles is almost certainly the city of choice.

ADVANCED TO FELLOWSHIP

Alford, Ralph I.	Montclair, New Jersey
Baer, Rudolf Louis	New York, New York
Brown, Frederick Robert	New York, New York
Buffum, William P.	Providence, Rhode Island
Cohen, Stanley	New Orleans, Louisiana
Ehret, Francis E.	Kenmore, New York
Fenton, Meryl Myron	Detroit, Michigan
Gaillard, G. Everett	Scarsdale, New York
Goodman, A. Albert	New York, New York
Jaffee, Isadore H.	Brighton, Massachusetts
Kraft, Bennett	Indianapolis, Indiana
Laws, Clarence L.	Atlanta, Georgia
London, McKinley	Cleveland Heights, Ohio
Lowell, Francis Cabot	Concord, Massachusetts
Manace, Bernard Abraham	Toronto, Ontario, Canada
Marton, Samuel	New York, New York

Merrill, George Adams	Brooklyn, New York
Messer, William	Brooklyn, New York
Miller, Malcolm W.	Philadelphia, Pennsylvania
Miller, William Lindsay	Gadsden, Alabama
Mulligan, Ralph Mitchell	Reading, Pennsylvania
Naterman, Hyman L.	Newton, Pennsylvania
Raynolds, Arthur H.	St. Petersburg, Florida
Ricchiuti, Joseph F.	Pottsville, Pennsylvania
Rose, Bram	Quebec, Canada
Sack, S. Senior	Flushing, New York
Samter, Max	Oak Park, Illinois
Schumacher, Irwin C.	San Francisco, California
Shure, Norman M.	Beverly Hills, California
Skwirsky, Joseph	Newark, New Jersey
Stuart, George J.	Washington, D. C.
Sutherland, Charles	Melbourne, Australia
Thomas, Clarence S.	Glenside, Pennsylvania
Vollmer, Earl S.	Glenside, Pennsylvania
Warren, Charles W.	Rochester, New York
Wilson, Keith S.	Clayton, Missouri

APPROVED FOR MEMBERSHIP

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Brown, Manuel	Tulsa, Oklahoma
Chernack, Morris J.	Bronx, New York
Cohen, Aaron Arthur	Hollywood, California
Curry, John J.	Arlington, Virginia
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Ehrlich, Edmund E.	Philadelphia, Pennsylvania
Estrada, de la Rive, G.	Havana, Cuba
Feingold, Ben F.	Beverly Hills, California
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Garat, Benigno Romulo	Buenos Aires, Argentina
Goldman, Harold I.	Denver, Colorado
Gordon, Benjamin F.	Chicago, Illinois
Grossman, Rubin	Bayonne, New Jersey
Hawver, Kenneth G.	Lima, Ohio
Hershey, Harold	Teaneck, New Jersey
Holtzman, Samuel George	South Fallsburg, New York
Jacobson, Seymour B.	New York, New York
Kelly, John F.	Brooklyn, New York
Leger, Jacques	Montreal, Quebec, Canada
Minden, Bendix S.	New York, New York
Morrow, Cecil S.	Kenosha, Wisconsin
Mullin, Harry	Scranton, Pennsylvania
Pearson, Catherine G.	Los Angeles, California

Rosenblum, Arthur H.	Chicago, Illinois
Rusch, Henry A., Jr.	New York, New York
Savage, Hugh J.	Lima, Ohio
Schirmer, Roy E.	Fort Smith, Arkansas
Schloss, Lewis J.	New York, New York
Scideman, Thomas	Brooklyn, New York
Sherman, Jerome	Baltimore, Maryland
Sievers, Jerome J.	Springfield, Illinois
Sones, Maurice	Philadelphia, Pennsylvania
Surinyach, Ramon	Barcelona, Spain
Swinny, Boen	San Antonio, Texas
Tuft, Harold S.	Philadelphia, Pennsylvania
Udkow, Samuel	New York, New York
Walzer, Eugene Harold	Bridgeport, Connecticut
Winer, Paul	New Haven, Connecticut
Witkov, Hyman Ronald	Montreal, Quebec, Canada

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Claus, Edward P.	Pittsburgh, Pennsylvania
Johnson, Mary Chapman	St. Louis, Missouri
Menzel, E. O. Arthur	Suffern, New York
Murray, Alan Thomas	Victoria, Australia

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Sir Henry Dale	England
Pasteur Vallery Radot	France

REPORT OF THE POLLEN SURVEY COMMITTEE OF THE AMERICAN ACADEMY OF ALLERGY

THEODORE L. SQUIER, M.D., CHAIRMAN
DATA COMPILED BY
OREN C. DURHAM, TECHNICAL DIRECTOR

The following data on pollen incidence during the seasons of 1946, 1947, and 1948 have been compiled from gravity slide figures submitted by research workers in various parts of the United States, Canada, and Mexico. In 1948 ragweed pollen incidence was heavier than in 1947 in Dallas, Nashville, Little Rock, and points in the vicinity of New York; but in most areas the count was lighter during the 1948 season. The date of highest incidence averaged about a week earlier than usual, occurring in many places as early as August 24. All figures except the "index"* are stated on the basis of the number of pollen grains per cubic yard of air. Names of collaborators are keyed into the ragweed table and listed below.

*The index figure is an arbitrary rating based on three factors: average length of season, maximum concentration, and average seasonal total. See Durham, O. C.: Evaluation of the Ragweed Hay Fever Resort Areas of North America, J. ALLERGY 8: 175, 1937.

RAGWEED POLLEN STUDIES MADE BY MEMBERS OF AND COLLABORATORS WITH THE POLLEN SURVEY COMMITTEE

STATE AND CITY	POLLEN GRAINS PER CU. YD. OF AIR — ANNUAL TOTALS 1946	1947	1948	MAXIMUM COUNT 1948	APEX DATE 1948	RAGWEED INDEX
Arizona						
Phoenix[1] (fall only)		17				0.06
Grand Canyon National Park[2]						
North Rim (fall only)			20	5	8/29	0.15
South Rim (fall only)		16				0.12
Arkansas						
Little Rock[3]		3,450	4,679	1,105	9/15	63.0
California						
Los Angeles[4]		60	119	11	10/7	0.71
Lassen Volcanic National Park[2]		3				0.03
Pasadena[5]		122				0.87
Sequoia National Park[2]		3				0.03
Yosemite National Park[2]		50				0.29
Colorado						
Colorado Springs[6]		1,324	1,104	101	8/27	27.0
Mesa Verde National Park[2]			97	9	9/3	0.52
Connecticut						
Bridgeport[7]			1,633	169	9/11	32.0
Fairfield[7]			1,391	115	9/13	26.0
Hartford[8]			3,321	239	8/23	54.0
New Haven[9]	1,906	856	1,354	109	8/29	30.0
Stratford[7]			1,222	122	9/11	26.0
Waterbury[10]	389	1,048	781	70	8/24	20.0
District of Columbia						
Washington[11]	2,158	2,108	2,330	262	8/29	40.0
Washington Airport[11]			2,154	344	8/31	35.0
Florida						
Miami Beach[12]			88	20	6/3	0.64
Georgia						
Atlanta[13]		1,420	1,584	187	9/17	30.0
Illinois						
Chicago[14]	4,116	7,526	4,017	364	8/26	75.0
Decatur[15]		9,660				114.0
Peoria[16]		13,071	10,324	961	8/30	108.0
Rockford[17]		9,471	6,569	525	8/26	100.0
Indiana						
Indianapolis[18]		6,655	7,591	526	8/28	100.0
Iowa						
Iowa City[19]	10,178	13,046	8,851	738	8/30	104.0
Kansas						
Goodland[2]		731				23.0
Maryland						
Bethesda[11]			5,755	1,038	8/25	65.0
Michigan						
Ann Arbor[19]		13,758	12,258	1,289	8/24	113.0
Detroit[20]		4,989	3,067	327	8/24	73.0
Montana						
Glacier National Park[2]						
Belton	11					0.10
Many Glacier	9					0.07

RAGWEED POLLEN STUDIES—CONT'D

STATE AND CITY	POLLEN GRAINS PER CU. YD. OF AIR					
	ANNUAL TOTALS			MAXIMUM COUNT	APEX DATE	RAGWEED INDEX
	1946	1947	1948	1948	1948	
Nebraska						
Omaha[21]		12,207	9,307	568	8/23	90.0
Nevada						
Lake Mead[2]		389				4.0
New Hampshire[22]						
Bath			185	47	9/6	3.0
Berlin		274	1,119	266	8/21	11.0
Charlestown			540	137	8/22	10.0
Colebrook		15	79	29	8/27	1.0
Concord		264	208	54	8/25	5.0
Errol			46	18	8/27	0.41
Exeter		329	2,069	788	8/26	26.0
Groveton			135	25	9/10	2.0
Hillsboro			189	50	8/27	4.0
Hinsdale			328	148	8/30	5.0
Keene		220	585	126	8/29	7.0
Laconia		29	1,073	594	8/31	12.0
Lebanon		4	1,797	274	8/26	17.0
Lincoln			217	36	8/30	3.0
Manchester			501	101	8/27	10.0
Nashua		137	2,542	569	8/29	20.0
New Ipswich			360	133	8/23	6.0
New London		0	177	32	8/29	1.0
North Conway		32	300	68	8/27	4.0
Ossipee			112	29	8/29	2.0
Pittsburg			87	18	8/25	0.61
Plymouth			201	43	8/28	4.0
Rochester			809	126	8/29	19.0
Rye			590	119	9/10	13.0
Warren		47	137	47	8/25	1.0
Whitefield		15	90	22	8/28	0.48
New Jersey						
Dover[23]			1,167	200	8/29	21.0
Freehold[23]			6,126	1,259	8/29	72.0
Maplewood[23]		1,998	1,003	135	8/25	17.0
New Brunswick[23]		830	7,036	2,770	8/31	63.0
Pitman[24]		3,995				51.0
Sandy Hook[23]			1,719	392	8/29	39.0
Teaneck[23]		1,809				31.0
Verona[23]	944	1,306	1,710	139	8/29	26.0
Westwood[23]			839	76	8/28	18.0
New Mexico						
Albuquerque[25]		97	674	194	9/13	10.0
New York						
Albany[26]	2,250	2,374	2,282	240		40.0
Ausable Forks[26]			872	112		20.0
Big Indian[26]						25.0
Big Moose[26]	260	242	296	30		8.0
Bronx[23]	1,203	1,121				26.0
Brooklyn[23]	853	1,043				20.0
Buffalo[27]	4,994	4,576	3,261	407	8/29	52.0
Croton[23]	1,163	1,728				29.0
East Berne[26]			1,604	104		32.0
Elsmere[26]						49.0
Fire Island[23]		1,072				23.0
Flushing[23, 28]	900	1,865	1,285	181	8/28	25.0
Garden City[23, 29]		1,198	1,437	285	8/29	27.0

RAGWEED POLLEN STUDIES—CONT'D

STATE AND CITY	POLLEN GRAINS PER CU. YD. OF AIR					
	ANNUAL TOTALS			MAXIMUM COUNT	APEX DATE	RAGWEED INDEX
	1946	1947	1948	1948	1948	
New York—cont'd						
Hague[26]	856	612	80	8		13.0
Haines Falls[26]						5.0
Hunter[26]			572	122		6.0
Indian Lake[26]		358	226	30		3.0
Jamaica[23]		1,596				35.0
Jamestown[26]	5,616					64.0
Keene Valley[26]		78	158	20		1.0
Lake Placid[26]	292		414	58		17.0
Long Lake[26]	206	218	278	46		3.0
Loon Lake[26]			204	36		5.0
Lowville[26]						20.0
Manhattan[23]	1,327	1,808				29.0
McKeever[26]		126	610	94		5.0
New York Metropolitan Average[23]	1,217	1,564	1,911	234	8/29	34.0
North Creek[26]	1,164	968	630	116		14.0
Northville[26]			746	166		14.0
Old Forge[26]						0.15
Paul Smith's[26]			300	30		7.0
Phoenicia[26]			2,116	268		31.0
Pine Hill[26]	340	396	378	58		6.0
Port Henry[26]			746	92		14.0
Plattsburg[26]	1,934	2,636				41.0
Remsen[26]	956	23,362	1,202	252		150.0
Rochester[30]	2,172	2,396	1,558	272	8/28	42.0
Rockaway[23]		1,515				27.0
Saranac Lake[26]			802	122		15.0
Shroon Lake[26]		290				4.0
Severence[26]			154	46		4.0
Speculator[26]	790	68	366	42		7.0
Staten Island[23]	1,350	1,906				27.0
Tannersville[26]	356	294	324	42		5.0
Tupper Lake[26]		428	352	52		13.0
Wanakena[26]	376	404	278	48		7.0
White Plains[23]		1,090	1,426	137	8/25	28.0
Windham[26]	1,722	46	2,782	544		20.0
Zena[26]		484	788	176		12.0
North Carolina						
Charlotte[31]		3,592	1,975	275	8/31	39.0
Ohio						
Akron[32]	10,011	8,772	7,030	1,105	8/29	94.0
Cleveland[33]	5,483	4,035	5,385	544	8/29	71.0
Toledo[34]	11,475	14,307	12,613	1,400	8/24	105.0
Youngstown[35]	4,741	5,063	4,511	551	8/30	62.0
Oregon						
Crater Lake National Park[2]		7				0.07
Pennsylvania						
Broomal[24]		2,208				40.0
Hatboro[24]		3,560				48.0
Philadelphia[24]	3,830	2,549	3,177	281	8/30	58.0
Pittsburgh[36]	6,600	3,449	7,619	756	8/26	60.0
Rhode Island						
Providence[37]		1,162	1,045	227	8/29	22.0
Tennessee						
Nashville[38]	9,470	4,488	6,168	558	8/31	60.0
Great Smoky Mts. National Park[2]						
Headquarters		582				13.0
Newfound Gap		204				4.0

RAGWEED POLLEN STUDIES—CONT'D

STATE AND CITY	POLLEN GRAINS PER CU. YD. OF AIR: ANNUAL TOTALS 1946	1947	1948	MAXIMUM COUNT 1948	APEX DATE 1948	RAGWEED INDEX
Texas						
Dallas[39]	13,523	21,810	25,543	1,969	9/25	146.0
Utah						
Bryce Canyon National Park[2]			148	14	9/15	0.88
Salt Lake City[40]		913	1,548	104	9/4	39.0
Zion National Park[2]		56	169	14	9/10	0.68
Vermont						
Burlington[41]			3,700	454	8/27	48.0
Virginia						
Shenandoah National Park[2]						
Headquarters			2,165	202	8/28	35.0
Big Meadows			638	94	8/30	10.0
Washington						
Olympic National Park[2]						
Headquarters (Elwha)		4	7	4	8/4	0.09
Hurricane Ridge			7	4	7/4	0.09
Wisconsin						
Madison[42]	4,620	14,946	4,725	588	8/24	105.0
Milwaukee[43]	9,916	11,656	6,688	1,159	8/25	97.0
Wyoming						
Grand Teton National Park[2]			14	4	7/11	0.11
Manitoba						
Winnipeg[44]		492	701	151	8/19	11.0
Ontario						
Hamilton[45]	5,772	12,618	4,688	498	8/27	62.0
Quebec						
Montreal[46]			1,353	189	9/9	20.0
Cuba						
Havana[47]		30				0.18
Mexico						
Mexico City[48]			745	40	7/28	16.0

1. Charles W. Vivian
2. Oren C. Durham
3. Alan G. Cazort
4. Abraham M. Targow
5. Willard S. Small
6. William C. Service
7. Eugene H. Walzer
8. Rose H. Klein and George Hurwitz
9. Barnett P. Freedman
10. Sidney W. Jennes
11. Eloise W. Kailin
12. Lewis Palay
13. John L. Jacobs
14. Theodore B. Bernstein
15. Helen C. Hayden
16. Leonard H. Harris
17. Nordahl O. Gunderson
18. Caryle B. Bohner
19. John M. Sheldon
20. Sidney Friedlaender and Alex S. Friedlaender
21. Ernest L. MacQuiddy
22. Frederick J. Vintinner (New Hampshire State Dept. of Health)
23. Matthew Walzer, Robert A. Chait, Eugene Walzer, Jerome Sherman, Bernard Siegel, and R. Wiseman
24. George I. Blumstein and Jay Spiegelman
25. Walter I. Werner
26. F. W. Gilcreas (New York State Dept. of Health)
27. Carl E. Arbesman
28. S. Senior Sack
29. Roland T. Jeffery
30. Jerome Glaser
31. Lester C. Todd
32. Karl D. Way
33. Harold J. Friedman

34. Karl D. Figley
35. Samuel R. Zoss
36. Leo H. Criep and T. H. Aaron
37. Francis H. Chafee
38. Edna S. Pennington
39. J. Harvey Black
40. Dean A. Moffat
41. Harold E. Medivetsky
42. William A. Mowry
43. Theodore L. Squier and Howard J. Lee
44. Charles H. A. Walton and Margaret G. Dudley
45. Robert F. Hughes
46. Howard S. Mitchell
47. Jose M. Quintero
48. Jose L. Cortes
49. Roland Rooks

In addition to the ragweed data noted above, a number of more complete reports on pollen incidence for 1948 were received. These will be discussed briefly.

Washington, D. C.: This study by Dr. Kailin includes complete differential counts from slides exposed in downtown Washington from February 1 to September 30, as well as differential counts from slides exposed during August and September on the roof of the station at the Washington National Airport. The tree pollen season began on February 18 and lasted approximately until May 20. The outstanding sources of tree pollen were elm, throughout March, sycamore and oak, throughout April. Paper mulberry was active for about two weeks during the latter part of April. Grass and English plantain pollens appeared during the second week of May, both continuing in very small amounts all through the summer. The heaviest months of grass pollination were, respectively, June, September, and May. Ragweed pollen constituted 90 per cent of the weed pollen content of the air during August and September.

Miami Beach, Florida: Dr. Palay's air testing began on November 1, 1947, and continued until September 30, 1948. Counting included all types of pollen. The incidence of Australian pine *(Casuarina spp.)* was much greater than that of all other pollens combined. Active pollination began on February 11, reached an extreme climax on February 23, and was light during April and early May. A second climax occurred on May 17, after which lesser amounts were found until about June 15. Stray granules of ragweed pollen were found during each of the ten months of the study. The maximum figure of 20 per cubic yard of air was reached on June 3. The extreme limit of ragweed pollination in southern Florida would seem to be May to December. Where ragweed pollen could originate from January to April is not apparent. At any rate, the total count for the year is very low and leaves Miami Beach with an index figure of less than 1, which is an excellent rating. The grass pollen season seems also to stretch throughout the whole year, with heaviest production in May.

Ann Arbor, Michigan (University Hospital): Daily exposures and differential pollen counts were made by Dr. Sheldon from April 1 to September 30. Elm pollen was very abundant throughout April. Box elder and other maples were active only during the last half of April. Oak, walnut, and hickory pollens appeared just before the middle of May and continued through the first week of June. Grass pollens appeared promptly on the first day of June and continued through July. Ragweed pollen constituted more than 99 per cent of the weed pollen recorded during August and September.

Omaha, Nebraska: Figures submitted by Dr. MacQuiddy cover the period of August 10 to September 20 only, and include ragweed, hemp, and amaranths. Hemp pollen was at least one-fifth as abundant as ragweed, with a climax figure of 146 per cubic yard on August 22. An appreciable amount of amaranth pollen was present in the air every day.

Albuquerque, New Mexico: In this study by Dr. Werner tests were made during every day of 1948. Only traces of unidentified or unimportant pollens were found before February

17. From that date elm pollen appeared in varying amounts almost daily until the end of March (maximum, 420 per cubic yard). The juniper pollen season began after the middle of March and lasted for about a month, with a maximum count of 500 pollen grains per cubic yard of air on March 28. The cottonwood season was confined almost wholly to April, with a climax on April 3. Small amounts of tamarix pollen were recorded during the latter half of April and occasionally during May. Grass pollens were noted from May 5 until November 1. The amounts were extremely small. Russian thistle appeared in small but consistent amounts in June, July, August, September, and early October. No ragweeds were noted before September 1. The season was definitely finished by the end of September. November and December yielded practically no pollen at all.

Garden City, New York: Differential counts during August and September by Dr. Jeffery showed appreciable amounts of grass pollen almost every day. Pigweed, lamb's-quarters, and plantain pollens, together with a few composites, constituted about 10 per cent of the fall weed pollen incidence.

Charlotte, North Carolina: Dr. Todd's study covered a period of nine months—February 1 to October 31. The tree pollen season opened on February 19 with appreciable amounts of cedar (juniper), alder, elm, and maple during the last week of February. The cedar season closed about the middle of March and alder, on March 4. Elm continued through March. Oak pollens first appeared on March 15 and reached a climax of 232 per cubic yard of air on March 24. Walnut, hickory, and pecan pollens were active from March 20 until the middle of May, with maximum figures for pecan on April 27. The grass season opened on April 3, with very few pollens recorded after the first week of July. The ragweed season opened on August 20 and continued until the first week of October, with only stray granules of any other kind of weed pollen during the ragweed season.

Cleveland, Ohio: Differential figures were reported by Dr. Friedman for May to September, inclusive. The study was started too late to include the season of active tree pollination. Grasses began during the last week of May and were scarce after July 21. Plantain pollens were recorded up to amounts of 50 per cubic yard of air almost every day from the middle of June until the first week of August. There was no appreciable amount of any pollen other than ragweed in the air during the ragweed season.

Toledo, Ohio: Dr. Figley's report covers a period of June to September, inclusive. Heavy incidence of grass pollen was noted throughout June and the first three weeks of July.

Pittsburgh, Pennsylvania: The complete counts for August and September reported by Drs. Criep and Aaron show only traces of plantain, grass, and cocklebur pollens. Ragweed constituted more than 99 per cent of the weed pollens reported.

Providence, Rhode Island: The statistics submitted by Dr. Chafee include ragweed, grass, and corn only. The latter two appeared frequently but in extremely small amounts.

Nashville, Tennessee: Dr. Pennington's tests were made from August 12 to October 23. Grass pollens in small amounts appeared daily from September 10 to 26. Annual sage *(Artemisia annua)* pollen grains appeared daily from September 10 to October 7, with a climax record of 100 per cubic yard of air on September 21. The proportion compared with ragweed was thus much smaller than has sometimes been recorded for this city. Pollen grains of the local fall blooming elm *(Ulmus serotina)* were fairly abundant during the same season as the grass and annual sage, namely, September 10 to October 10. The maximum figure was 45 per cubic yard of air on September 12.

Salt Lake City, Utah: Complete counts for April to September, inclusive, 1947 and 1948, by Dr. Moffat, allow a comparison of the proportions of the principal pollens, ragweed, chenopod, and sagebrush. Totals were as follows:

	1947	1948
Ragweed	913	1,548
Chenopod	411	554
Sagebrush	1,100	309

Cottonwood and box elder were active in April both years. No other tree pollens were numerous except alder, which was abundant, for about a week in April. Grasses appeared in early April in 1947, but not until May 13 in 1948. Grass figures were low after June. Russian thistle began both years about July 10, with the climax in late August. Russian thistle and kochia pollen grains appeared in about equal proportions both seasons.

Milwaukee, Wisconsin: Figures are complete from April to September, inclusive. Drs. Squier and Lee found small but consistent amounts of elm and maple (including box elder) pollens during all of April and the first week of May. Oak appeared on May 4, with a maximum of about 150 on May 21. Of the tree pollens only hickory lasted beyond May. The grass season began on May 18, with low counts until June 1, a maximum of 100 on June 25, and with small but consistent amounts through July. Ragweed pollen, including a few grains each of cocklebur and burweed marsh elder, constituted more than 99 per cent of the weed pollen content of the air during August and September.

Winnipeg, Manitoba: Drs. Walton and Dudley have reported complete counts for July, August, September, and October. During this period ragweed pollen constituted 87 per cent of the weed pollen content of the air. Grass pollens were extremely rare throughout. Stray ragweed granules were found as early as July 6 but most of the catch was obtained in August. Chenopod pollens constituted 7 per cent of the total weed pollen incidence. Sagebrush pollens totaled only 22 for the whole season.

Hamilton, Ontario: This study by Dr. Hughes covered the months of June, July, August and September. The grass season occurred in June and July, with heaviest incidence from June 29 to July 20. No weed pollens other than those of ragweed appeared in significant amounts at any time.

Mexico City, Mexico: Complete counts were made for one year beginning November, 1947. The seasons and the portions of all pollens reported on this study by Dr. Cortes correspond closely with those established by Dr. Salazar Mallen as reported in 1940. Ash, cedar *(Cupressus),* and alder began to shed small amounts of pollen immediately after the rainy season. The first two named began as early as September. All three pollinated throughout the winter, reaching climaxes for ash in February, and for cedar and alder in December. The oak season ran from February to early April. Bermuda grass appeared in very small amounts in March and in increasing amounts through April, with a climax in May; stray granules continued until the end of September. The ragweed figures, including marsh elder *(Iva ciliata),* show a season lasting from early June until the end of October, with most of the pollen appearing in late July and August. The amount is much larger than was recorded in the survey conducted by Durham in 1932 and 1933.

ANNOUNCEMENTS

A postgraduate course on "Diseases Due to Allergic and Immune Mechanisms," sponsored by the American College of Physicians and approved by the American Academy of Allergy, will be given in Atlantic City, April 28 to May 1.

This will precede the meetings of the American Society for Clinical Investigation and the Association of American Physicians which will be held May 2 to 4.

Inquiries should be addressed to Mr. E. R. Loveland, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

Officers of Instruction

HARRY L. ALEXANDER, M.D., F.A.C.P., Professor of Clinical Medicine, Washington University School of Medicine; Associate Physician, Barnes Hospital; St. Louis, Mo.

RUDOLF L. BAER, M.D., Assistant Professor of Clinical Dermatology and Syphilology, Post-Graduate Medical School, and Attending Dermatologist and Syphilologist, University Hospital, New York University—Bellevue Medical Center, New York, N. Y.

GEORGE I. BLUMSTEIN, M.D., Associate in Medicine, Temple University School of Medicine; Chief, Allergy Clinic, Mount Sinai Hospital; Philadelphia, Pa.

MAURICE BRUGER, M.D., F.A.C.P., Associate Professor of Medicine, Post-Graduate Medical School, and Chief, Division of Pathological Chemistry, University Hospital, New York University—Bellevue Medical Center, New York, N. Y.

MERRILL W. CHASE, Ph.D., Member of Staff, Rockefeller Institute for Medical Research, New York, N. Y.

LEO H. CRIEP, M.D., Associate Professor of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

ELVIN A. KABAT, Ph.D., Associate Professor of Bacteriology, Columbia University College of Physicians and Surgeons, New York, N. Y.

PAUL KLEMPERER, M.D., Professor of Pathology, Columbia University College of Physicians and Surgeons; Pathologist, Mount Sinai Hospital; New York, N. Y.

PHILIP LEVINE, M.D., F.A.C.P., Director, Biological Division, Ortho Research Foundation, Raritan, N. J.

R. L. MAYER, M.D., Chief Microbiologist and Head, Microbiology Division, Ciba Pharmaceutical Products, Inc., Summit, N. J.

CAMPBELL MOSES, JR., M.D., Assistant Professor of Medicine, and Director, Addison H. Gibson Laboratory of Applied Physiology, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

GEORGE E. ROCKWELL, M.D., Member of Staffs, Bethesda and Our Lady of Mercy Hospitals, Cincinnati; Milford, Ohio.

HARRY P. SCHENCK, M.D., F.A.C.S., Professor of Otolaryngology, University of Pennsylvania School of Medicine; Chief, Otolaryngologic Clinic, Hospital of the University of Pennsylvania; Philadelphia, Pa.

ELMER L. SEVRINGHAUS, M.D., F.A.C.P., Director of Clinical Research, Hoffmann-La Roche, Inc.; Member, Foods and Nutrition Board, National Research Council; Nutley, N. J.

WILLIAM B. SHERMAN, M.D., F.A.C.P., Associate in Medicine, Columbia University College of Physicians and Surgeons; Attending Physician, Presbyterian and Roosevelt Hospitals; New York, N. Y.

MARION B. SULZBERGER, M.D., Professor of Dermatology and Syphilology, Post-Graduate Medical School, New York University—Bellevue Medical Center; Director, Department of Dermatology and Syphilology, New York Skin and Cancer Unit; New York, N. Y.

LOUIS TUFT, M.D., Assistant Professor of Medicine, Temple University School of Medicine; Chief, Clinic of Allergy and Applied Immunology, Temple University Hospital; Philadelphia, Pa.

MATTHEW WALZER, M.D., Attending Physician, Jewish Hospital, Brooklyn, N. Y.

Outline of Course

Thursday, April 28.

A.M. Session.

9:00-11:00 Fundamental Concepts of Immunity. Immunochemistry of Antigen-Antibody Reactions.
Dr. Kabat.

11:00-12:00 The Chemical Nature of Allergens.
Dr. Rockwell.

P.M. Session.

1:00-3:00 Applied Immunology in Allergic Disorders.
Dr. Sherman.

3:00-4:00 Clinical Manifestations of Iso-Immunization by the Rh Factor.
Dr. Levine.

4:00-5:00 Round Table.
Drs. Criep, Kabat, Rockwell, Sherman, and Levine.

Friday, April 29.

A.M. Session.

9:00-10:00 The Physiology of Allergic Reactions.
Dr. Moses.

10:00-11:00 The Pharmacological Action of Drugs Used in Allergy.
Dr. Bruger.

11:00-12:00 The Role of Histamine in Allergy; Antihistaminic Agents.
Dr. Mayer.

P.M. Session.

1:00-2:00 Critical Interpretation of Allergic Skin Reactions.
Dr. Walzer.

2:00-3:00 Allergy to Fungi.
Dr. Blumstein.

3:00-4:00 Rhinology in Relation to Allergy.
Dr. Schenck.

4:00-5:00 Round Table.
Drs. Criep, Moses, Bruger, Mayer, Walzer, Blumstein, and Schenck.

Saturday, April 30.

A.M. Session.

9:00-10:30 Allergic Dermatoses: Atopic Dermatitis; Contact Dermatitis; Dermophytids.
Drs. Sulzberger and Baer.

10:30-11:30 Allergy to Drugs and Antibiotics.
Dr. Tuft.

11:30-12:00 Immunology of Allergic Dermatoses.
Drs. Sulzberger and Baer.

P.M. Session.

1:00-1:30 Immunology of Allergic Dermatoses (continued).
Drs. Sulzberger and Baer.

1:30-3:00 Allergy to Chemicals. Experimental Approach.
Dr. Chase.

3:00-4:00 Cross Sensitization.
Dr. Mayer.
4:00-5:00 Round Table.
Drs. Criep, Sulzberger, Baer, Tuft, Chase, and Mayer.

Sunday, May 1.

A.M. Session.

9:00-10:00 Serum Allergy.
Dr. Tuft.
10:00-11:00 Allergy Due to Infectious Agents.
Dr. Alexander.
11:00-11:30 Collagen Disease in Relation to Allergy.
Dr. Criep.
11:30-12:00 Endocrine and Nutritional Factors in Allergy.
Dr. Sevringhaus.

P.M. Session.

1:00-2:00 The Pathology of Allergic Reactions.
Dr. Klemperer.
2:00-3:00 Clinical Correlation of Allergic Disorders.
Dr. Alexander.
3:00-4:00 Round Table.
Drs. Criep, Tuft, Alexander, Sevringhaus, and Klemperer.

The American College of Allergists will hold its annual meeting at the Palmer House, Chicago, from Thursday, April 14 through Sunday, April 17, 1949. Inquiry concerning details of the meeting should be addressed to Dr. Fred W. Wittich, 423 LaSalle Medical Building, Minneapolis, Minnesota.